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Bescheinigung | Certificate | Attestation

#52

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

00200452.1

PRIORITY DOCUMENT
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Der Präsident des Europäischen Patentamts;
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For the President of the European Patent Office

Le Président de l'Office européen des brevets
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I.L.C. HATTEN-HECKMAN

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Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

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Application no.: 00200452.1
Demande n°:

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Date of filing: 11/02/00
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Anmelder:
Applicant(s):
Demandeur(s):
JANSSEN PHARMACEUTICA N.V.
2340 Beerse
BELGIUM

Bezeichnung der Erfindung:
Title of the invention:
Titre de l'invention:
Respiratory syncytial virus replication inhibitors

In Anspruch genommene Priorität(en) / Priority(ies) claimed / Priorité(s) revendiquée(s)

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RESPIRATORY SYNCYTIAL VIRUS REPLICATION INHIBITORS

The present invention is concerned with benzimidazoles and imidazopyridines having antiviral activity, in particular, they have an inhibitory activity on the replication of the respiratory syncytial virus. It further concerns their preparation and compositions comprising them, as well as their use as a medicine.

Human RSV or Respiratory Syncytial Virus is a large RNA virus, member of the family of Paramyxoviridae, subfamily pneumovirinae together with bovine RSV virus. Human RSV is responsible for a spectrum of respiratory tract diseases in people of all ages throughout the world. It is the major cause of lower respiratory tract illness during infancy and childhood. Over half of all infants encounter RSV in their first year of life, and almost all within their first two years. The infection in young children can cause lung damage that persists for years and may contribute to chronic lung disease in later life (chronic wheezing, asthma). Older children and adults often suffer from a (bad) common cold upon RSV infection. In old age, susceptibility again increases, and RSV has been implicated in a number of outbreaks of pneumonia in the aged resulting in significant mortality.

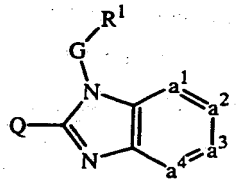
Infection with a virus from a given subgroup does not protect against a subsequent infection with an RSV isolate from the same subgroup in the following winter season. Re-infection with RSV is thus common, despite the existence of only two subtypes, A and B.

Today only three drugs have been approved for use against RSV infection. Ribavirin, a nucleoside analogue, provides an aerosol treatment for serious RSV infection in hospitalized children. The aerosol route of administration, the toxicity (risk of teratogenicity), the cost and the highly variable efficacy limit its use. The other two drugs, RespiGam® and palivizumab, polyclonal and monoclonal antibody immunostimulants, are intended to be used in a preventive way.

Other attempts to develop a safe and effective RSV vaccine have all met with failure thus far. Inactivated vaccines failed to protect against disease, and in fact in some cases enhanced disease during subsequent infection. Life attenuated vaccines have been tried with limited success. Clearly there is a need for an efficacious non-toxic and easy to administer drug against RSV replication.

EP-A-0,099,139 , EP-A-0,099,139 , EP-A-0,145,037 , EP-A-0,144,101 , EP-A-0,151,826 , EP-A-0,151,824 , EP-A-0,232,937 , EP-A-0,295,742 , EP 0,297,661 , EP-A-0,307,014 , WO 92 01697 describe benzimidazole and imidazopyridine substituted piperidine and piperazine derivatives as antihistaminics, antiallergics or serotonine antagonists.

The present invention concerns the use of a compound for the manufacture of a medicament for treating viral infections, wherein the compound is a compound of formula



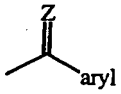
(I)

a prodrug, *N*-oxide, addition salt, quaternary amine, metal complex and stereochemically isomeric form thereof, wherein

$-a^1=a^2-a^3=a^4-$ represents a bivalent radical of formula

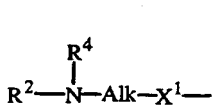
-CH=CH-CH=CH-	(a-1);
-N=CH-CH=CH-	(a-2);
-CH=N-CH=CH-	(a-3);
-CH=CH-N=CH-	(a-4); or
-CH=CH-CH=N-	(a-5);

wherein each hydrogen atom in the radicals (a-1), (a-2), (a-3), (a-4) and (a-5) may optionally be replaced by halo, C_{1-6}alkyl, nitro, amino, hydroxy, C_{1-6}alkyloxy, polyhaloC_{1-6}alkyl, carboxyl, aminoC_{1-6}alkyl, mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, hydroxyC_{1-6}alkyl, or a radical of formula

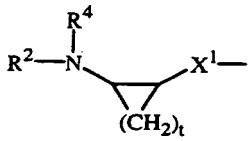


wherein =Z is =O, $=CH-C(=O)-NR^{5a}R^{5b}$, $=CH_2$, $=CH-C_{1-6}$alkyl, =N-OH or $=N-O-C_{1-6}$alkyl;

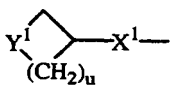
Q is a radical of formula



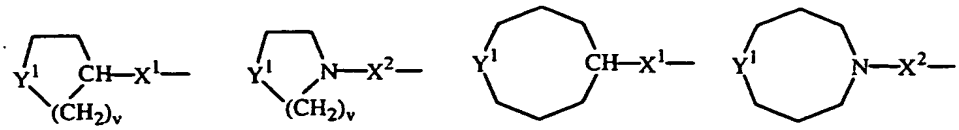
(b-1)



(b-2)



(b-3)



(b-4) (b-5) (b-6) (b-7)

wherein Alk is C_{1-6}alkanediyl;

Y^1 is a bivalent radical of formula $-NR^2-$ or $-CH(NR^2R^4)-$;

X^1 is NR^4, S, S(=O), $S(=O)_2$, O, CH_2, C(=O), $C(=CH_2)$, CH(OH), $CH(CH_3)$, $CH(OCH_3)$, $CH(SCH_3)$, $CH(NR^{5a}R^{5b})$, CH_2-NR^4 or NR^4-CH_2;

X^2 is a direct bond, CH_2 or C(=O);

t is 2, 3, 4 or 5;

u is 1, 2, 3, 4 or 5;

v is 2 or 3; and

whereby each hydrogen atom in Alk and the carbocycles and the heterocycles defined in radicals (b-2), (b-3), (b-4), (b-5), (b-6) and (b-7) may optionally be replaced by R^3; with the proviso that when R^3 is hydroxy or C_{1-6}alkyloxy, then R^3 can not replace a hydrogen atom in the α position relative to a nitrogen atom;

G is a direct bond or C_{1-10}alkanediyl;

R^1 is a monocyclic heterocycle selected from pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyrrolyl, imidazolyl and pyrazolyl; and each heterocycle may optionally be substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5a}-, aryl-SO_2-NR^{5a}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5a}R^{5b}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-;

each n independently is 1, 2, 3 or 4;

R^2 is hydrogen, pyrrolidinyl, piperidinyl, homopiperidinyl, C_{3-7}cycloalkyl substituted with NHR^6, or C_{1-10}alkyl substituted with NHR^6 and optionally with a second, third or fourth substituent selected from amino, hydroxy, C_{3-7}cycloalkyl, C_{2-5}alkanediyl, piperidinyl, mono-or di(C_{1-6}alkyl)amino, C_{1-6}alkyloxycarbonylamino, aryl and aryloxy;

R^3 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy or arylC_{1-6}alkyl;

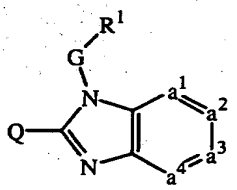
R^4 is hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl;

R^{5a} and R^{5b} each independently are hydrogen or C_{1-6}alkyl; or

R^{5a} and R^{5b} taken together from a bivalent radical of formula $-(CH_2)_s-$ wherein s is 4 or 5;
R^6 is hydrogen, C_{1-4}alkyl, formyl, C_{1-6}alkylcarbonyl or C_{1-6}alkyloxycarbonyl;
aryl is phenyl or phenyl substituted with 1 or more, such as 2, 3 or 4, substituents selected from halo, hydroxy, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, polyhaloC_{1-6}alkyl, and C_{1-6}alkyloxy.

The present invention also relates to a method of treating warm-blooded animals suffering from viral infections, in particular RSV infection. Said method comprises the administration of a therapeutically effective amount of a compound of formula (I) or a prodrug thereof, a *N*-oxide form, a pharmaceutically acceptable acid or base addition salt, a quaternary amine, a metal complex or a stereochemically isomeric form thereof in admixture with a pharmaceutical carrier.

A further embodiment of the present invention includes the compounds of formula (I)

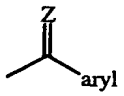


(I)

their prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms, wherein
$-a^1=a^2-a^3=a^4-$ represents a radical of formula

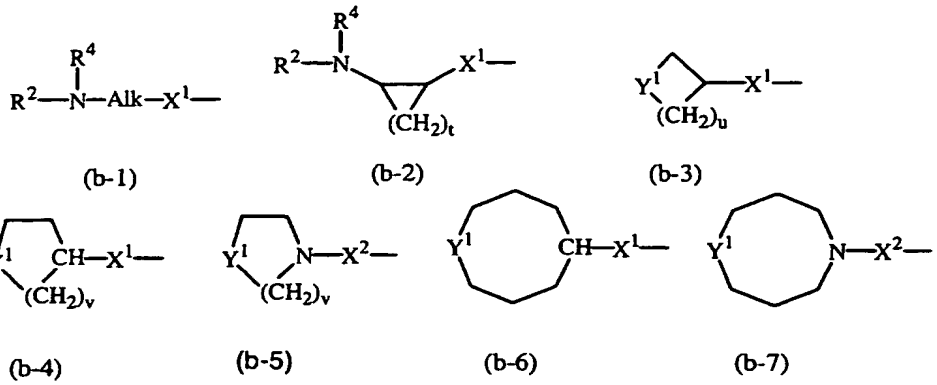
-CH=CH-CH=CH-	(a-1);
-N=CH-CH=CH-	(a-2);
-CH=N-CH=CH-	(a-3);
-CH=CH-N=CH-	(a-4); or
-CH=CH-CH=N-	(a-5);

wherein each hydrogen atom in the radicals (a-1), (a-2), (a-3), (a-4) and (a-5) may optionally be replaced by halo, C_{1-6}alkyl, nitro, amino, hydroxy, C_{1-6}alkyloxy, polyhaloC_{1-6}alkyl, carboxyl, aminoC_{1-6}alkyl, mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, hydroxyC_{1-6}alkyl, or a radical of formula



wherein =Z is =O, =CH-C(=O)-$NR^{5a}R^{5b}$, $=CH_2$, =CH-C_{1-6}alkyl, =N-OH or =N-O-C_{1-6}alkyl;

Q is a radical of formula



(b-1) (b-2) (b-3)

(b-4) (b-5) (b-6) (b-7)

wherein Alk is C_{1-6}alkanediyl;

Y^1 is a bivalent radical of formula $-NR^2-$ or $-CH(NR^2R^4)-$;

X^1 is NR^4, S, S(=O), $S(=O)_2$, O, CH_2, C(=O), $C(=CH_2)$, CH(OH), $CH(CH_3)$, $CH(OCH_3)$, $CH(SCH_3)$, $CH(NR^{5a}R^{5b})$, CH_2-NR^4 or NR^4-CH_2;

X^2 is a direct bond, CH_2 or C(=O);

t is 2, 3, 4 or 5;

u is 1, 2, 3, 4 or 5;

v is 2 or 3; and

whereby each hydrogen atom in Alk and the carbocycles and the heterocycles defined in radicals (b-2), (b-3), (b-4), (b-5), (b-6) and (b-7) may optionally be replaced by R^3; with the proviso that when R^3 is hydroxy or C_{1-6}alkyloxy, then R^3 can not replace a hydrogen atom in the α position relative to a nitrogen atom;

G is a direct bond or C_{1-10}alkanediyl;

R^1 is a monocyclic heterocycle selected from pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyrrolyl, imidazolyl and pyrazolyl; and each heterocycle may optionally be substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkyl-carbonylamino, C_{1-6}alkyl-SO_2-NR^{5a}-, aryl-SO_2-NR^{5a}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5a}R^{5b}$, $HO(-CH_2-CH_2-O)_n$-, halo$(-CH_2-CH_2-O)_n$-, C_{1-6}alkyloxy$(-CH_2-CH_2-O)_n$-, arylC_{1-6}alkyloxy$(-CH_2-CH_2-O)_n$- and mono-or di(C_{1-6}alkyl)amino$(-CH_2-CH_2-O)_n$-;

each n independently is 1, 2, 3 or 4;

R^2 is hydrogen, pyrrolidinyl, piperidinyl, homopiperidinyl, C_{3-7}cycloalkyl substituted with NHR^6, or C_{1-10}alkyl substituted with NHR^6 and optionally with a second, third or fourth substituent selected from amino, hydroxy, C_{3-7}cycloalkyl, C_{2-5}alkanediyl, piperidinyl, mono-or di(C_{1-6}alkyl)amino, C_{1-6}alkyloxycarbonylamino, aryl and aryloxy;

R^3 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy or arylC_{1-6}alkyl;

R^4 is hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl;

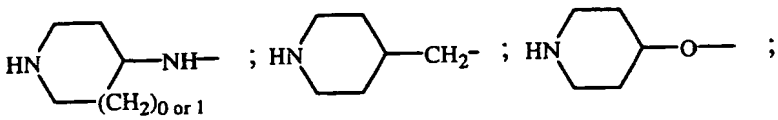
R^{5a} and R^{5b} each independently are hydrogen or C_{1-6}alkyl; or

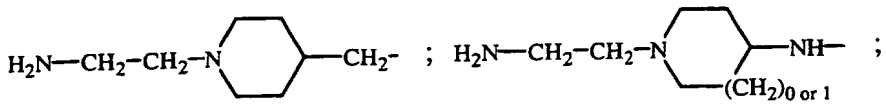
R^{5a} and R^{5b} taken together from a bivalent radical of formula $-(CH_2)_s-$ wherein s is 4 or 5;

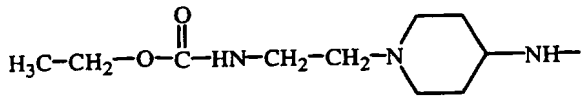
R^6 is hydrogen, C_{1-4}alkyl, formyl, C_{1-6}alkylcarbonyl or C_{1-6}alkyloxycarbonyl;

aryl is phenyl or phenyl substituted with 1 or more, such as 2, 3 or 4, substituents selected from halo, hydroxy, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, polyhaloC_{1-6}alkyl, and C_{1-6}alkyloxy;

provided that when G is methylene, and R^1 is 2-pyridyl, 3-pyridyl, 6-methyl-2-pyridyl, 2-pyrazinyl or 5-methyl-imidazol-4-yl, and $-a^1=a^2-a^3=a^4-$ is $-CH=CH-CH=CH-$ or $-N=CH-CH=CH-$, then Q is other than







The term prodrug as used throughout this text means the pharmacologically acceptable derivatives, e.g. esters and amides, such that the resulting biotransformation product of the derivative is the active drug as defined in the compounds of formula (I). The reference by Goodman and Gilman (The Pharmacological Basis of Therapeutics, 8th ed., McGraw-Hill, Int. Ed. 1992, "Biotransformation of Drugs", p. 13-15) describing prodrugs generally, is hereby incorporated.

As used herein C_{1-4}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as methyl, ethyl, propyl, 1-methylethyl, butyl and the like; C_{1-6}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as the groups defined for C_{1-4}alkyl and pentyl, hexyl, 2-methylpropyl, 2-methylbutyl and the like; C_{1-9}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 9 carbon atoms such as the groups defined for C_{1-6}alkyl and heptyl, octyl, nonyl, 2-methylhexyl, 2-methylheptyl and the like; C_{1-10}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 10 carbon atoms such as the groups

defined for C_{1-9}alkyl and decyl, 2-methylnonyl and the like. C_{3-7}cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl; C_{2-5}alkanediyl defines bivalent straight and branched chain saturated hydrocarbon radicals having from 2 to 5 carbon atoms such as, for example, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,2-propanediyl, 2,3-butanediyl, 1,5-pentanediyl and the like, C_{2-5}alkanediyl is substituted on C_{1-10}alkyl as provided for in the definition of R^2, it is meant to be substituted on one carbon atom thus forming a spiro moiety; C_{1-4}alkanediyl defines bivalent straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl and the like; C_{1-6}alkanediyl is meant to include C_{1-4}alkanediyl and the higher homologues thereof having from 5 to 6 carbon atoms such as, for example, 1,5-pentanediyl, 1,6-hexanediyl and the like; C_{1-10}alkanediyl is meant to include C_{1-6}alkanediyl and the higher homologues thereof having from 7 to 10 carbon atoms such as, for example, 1,7-heptanediyl, 1,8-octanediyl, 1,9-nonanediyl, 1,10-decanediyl and the like.

As used herein before, the term (=O) forms a carbonyl moiety when attached to a carbon atom, a sulfoxide moiety when attached to a sulfur atom and a sulfonyl moiety when two of said terms are attached to a sulfur atom. The term (=NOH) forms a hydroxylimine moiety when attached to a carbon atom.

The term halo is generic to fluoro, chloro, bromo and iodo. As used in the foregoing and hereinafter, polyhaloC_{1-6}alkyl as a group or part of a group is defined as mono- or polyhalosubstituted C_{1-6}alkyl, in particular methyl with one or more fluoro atoms, for example, difluoromethyl or trifluoromethyl. In case more than one halogen atoms are attached to an alkyl group within the definition of polyhaloC_{1-4}alkyl, they may be the same or different.

When any variable (e.g. aryl, R^2, R^3, R^4, R^{5a}, R^{5b} etc.) occurs more than one time in any constituent, each definition is independent.

It will be appreciated that some of the compounds of formula (I) and their prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms may contain one or more centers of chirality and exist as stereochemically isomeric forms.

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible stereoisomeric forms which the compounds of formula (I), and their prodrugs,

N-oxides, addition salts, quaternary amines, metal complexes or physiologically functional derivatives may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure as well as each of the individual isomeric forms of formula (I) and their prodrugs, *N*-oxides, salts, solvates, quaternary amines, metal complexes substantially free, *i.e.* associated with less than 10%, preferably less than 5%, in particular less than 2% and most preferably less than 1% of the other isomers. Stereochemically isomeric forms of the compounds of formula (I) are obviously intended to be embraced within the scope of this invention.

For some of the compounds of formula (I), their prodrugs, *N*-oxides, salts, solvates, quaternary amines or metal complexes and the intermediates used in the preparation thereof, the absolute stereochemical configuration was not experimentally determined. In these cases the stereoisomeric form which was first isolated is designated as "A" and the second as "B", without further reference to the actual stereochemical configuration. However, said "A" and "B" stereoisomeric forms can be unambiguously characterized by for instance their optical rotation in case "A" and "B" have an enantiomeric relationship. A person skilled in the art is able to determine the absolute configuration of such compounds using art-known methods such as, for example, X-ray diffraction. In case "A" and "B" are stereoisomeric mixtures, they can be further separated whereby the respective first fractions isolated are designated "A1" and "B1" and the second as "A2" and "B2", without further reference to the actual stereochemical configuration.

For therapeutic use, salts of the compounds of formula (I) are those wherein the counterion is pharmaceutically acceptable. However, salts of acids and bases which are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound. All salts, whether pharmaceutically acceptable or not are included within the ambit of the present invention.

The pharmaceutically acceptable acid and base addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid and base addition salt forms which the compounds of formula (I) are able to form. The pharmaceutically acceptable acid addition salts can conveniently be obtained by treating the base form with such appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic,

hydroxyacetic, lactic, pyruvic, oxalic (i.e. ethanedioic), malonic, succinic (i.e. butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids.

Conversely said salt forms can be converted by treatment with an appropriate base into the free base form.

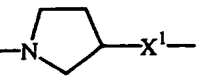
The compounds of formula (I) containing an acidic proton may also be converted into their non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

The term addition salt as used hereinabove also comprises the solvates which the compounds of formula (I) as well as the salts thereof, are able to form. Such solvates are for example hydrates, alcoholates and the like.

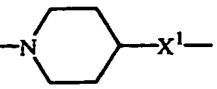
It will be appreciated that the compounds of formula (I) may have metal binding, chelating, complexating properties and therefore may exist as metal complexes or metal chelates. Such metalated derivatives of the compounds of formula (I) are intended to be included within the scope of the present invention.

Some of the compounds of formula (I) may also exist in their tautomeric form. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

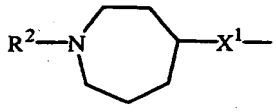
A special group of compounds are those compounds of formula (I) wherein the following restrictions apply :

when Q is 

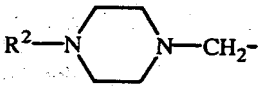
wherein X^1 is NR^4, O, S, S(=O), $S(=O)_2$, CH_2, C(=O), $C(=CH_2)$ or $CH(CH_3)$, then R^1 is other than pyridyl, pyridyl substituted with C_{1-6}alkyl, pyrimidinyl, pyrazinyl, imidazolyl and imidazolyl substituted with C_{1-6}alkyl;

when Q is 

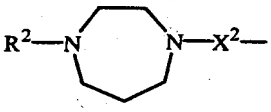
wherein X^1 is NR^4, O, S, S(=O), $S(=O)_2$, CH_2, C(=O), $C(=CH_2)$ or $CH(CH_3)$, then R^1 is other than pyridyl, pyridyl substituted with C_{1-6}alkyl, pyridyl substituted with 1 or 2 C_{1-6}alkyloxy, pyrazinyl, pyrrolyl, pyrrolyl substituted with C_{1-6}alkyl, imidazolyl and imidazolyl substituted with C_{1-6}alkyl;

when Q is 

wherein X^1 is NR^4, O, S, S(=O), $S(=O)_2$, CH_2, C(=O), $C(=CH_2)$ or $CH(CH_3)$, then R^1 is other than pyridyl, pyridyl substituted with C_{1-6}alkyl, pyrimidinyl, pyrazinyl, imidazolyl and imidazolyl substituted with C_{1-6}alkyl;

when Q is 

then R^1 is other than pyridyl, pyrimidinyl, pyrazinyl, imidazolyl and imidazolyl substituted with C_{1-6}alkyl;

when Q is 

wherein X^2 is CH_2 or a direct bond, then R^1 is other than pyridyl, pyridyl substituted with C_{1-6}alkyl, pyrimidinyl, pyrazinyl, imidazolyl and imidazolyl substituted with C_{1-6}alkyl.

Or a special group of compounds are those compounds of formula (I) wherein one of the following applies :

Q is a radical of formula (b-1); (b-2); (b-4); (b-5); (b-6); (b-7); (b-3) wherein u is 1,3,4 or 5; or (b-3) wherein u is 2, wherein Y^1 is $-CH(NR^2R^4)-$, wherein X^1 is CH(OH), $CH(OCH_3)$, $CH(SCH_3)$, $CH(NR^{5a}R^{5b})$, CH_2-NR^4 or NR^4-CH_2, and wherein R^1 is pyridyl or imidazolyl, each of said heterocycles substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5a}-, aryl-SO_2-NR^{5a}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5a}R^{5b}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-, or each of said heterocycles substituted with, where possible 2, 3 or 4 C_{1-6}alkyl groups, or wherein R^1 is pyrimidinyl or pyrazinyl, each of said heterocycles being substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy,

hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5a}-, aryl-SO_2-NR^{5a}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5a}R^{5b}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-; or wherein R^1 is pyrrolyl or pyrazolyl, each of said heterocycles optionally being substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5a}-, aryl-SO_2-NR^{5a}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5a}R^{5b}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-; or

Q is a radical of formula (b-1); (b-2); (b-3); (b-5); (b-6); (b-7); (b-4) wherein v is 3; or (b-4) wherein v is 2, wherein Y^1 is –CH(NR^2R^4)-, wherein X^1 is CH(OH), CH(OCH_3), CH(SCH_3), CH($NR^{5a}R^{5b}$), CH_2-NR^4 or NR^4-CH_2, and wherein R^1 is pyrrolyl or imidazolyl, each of said heterocycles substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxy-C_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5a}-, aryl-SO_2-NR^{5a}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5a}R^{5b}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-, or each of said heterocycles substituted with, where possible 2, 3 or 4 C_{1-6}alkyl groups; or wherein R^1 is pyridyl substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5a}-, aryl-SO_2-NR^{5a}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5a}R^{5b}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-, or pyridyl substituted with, 2, 3 or 4 C_{1-6}alkyl groups or 3 or 4 C_{1-6}alkyloxy groups; or wherein R^1 is pyrazinyl substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or

di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5a}-, aryl-SO_2-NR^{5a}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5a}R^{5b}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-; or wherein R^1 is pyridazinyl, pyrimidinyl or pyrazolyl, each of said heterocycles optionally being substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5a}-, aryl-SO_2-NR^{5a}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5a}R^{5b}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-; or

Q is a radical of formula (b-1); (b-2); (b-3); (b-5); (b-6); (b-7); (b-4) wherein v is 2; or (b-4) wherein v is 3, wherein Y^1 is –CH(NR^2R^4)-, wherein X^1 is CH(OH), CH(OCH_3), CH(SCH_3), CH($NR^{5a}R^{5b}$), CH_2-NR^4 or NR^4-CH_2, and wherein R^1 is pyridyl or imidazolyl, each of said heterocycles substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxy-C_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5a}-, aryl-SO_2-NR^{5a}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5a}R^{5b}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-, or each of said heterocycles substituted with, where possible 2, 3 or 4 C_{1-6}alkyl groups; or wherein R^1 is pyrimidinyl or pyrazinyl, each of said heterocycles being substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5a}-, aryl-SO_2-NR^{5a}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5a}R^{5b}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-; or wherein R^1 is pyrrolyl or pyrazolyl, each of said heterocycles optionally being substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy,

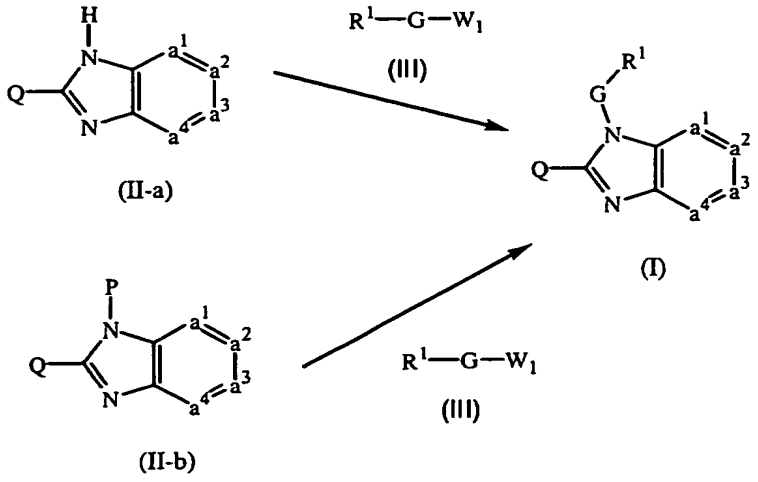
hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5a}-, aryl-SO_2-NR^{5a}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5a}R^{5b}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-; or

Q is a radical of formula (b-1); (b-2); (b-3); (b-4); (b-6); (b-7); (b-5) wherein v is 3; or (b-5) wherein v is 2, wherein Y^1 is –CH(NR^2R^4)-, wherein X^2 is a direct bond or C(=O), wherein R^1 is pyridyl, pyrimidinyl, pyrazinyl, each of said heterocycles being substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxy-C_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)-amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonyl-amino, C_{1-6}alkyl-SO_2-NR^{5a}-, aryl-SO_2-NR^{5a}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5a}R^{5b}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-, or wherein R^1 is imidazolyl substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5a}-, aryl-SO_2-NR^{5a}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5a}R^{5b}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-, or each of said heterocycles substituted with, where possible 2, 3 or 4 C_{1-6}alkyl groups, or wherein R^1 is pyridazinyl, pyrrolyl, or pyrazolyl, each of said heterocycles optionally being substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)-aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5a}-, aryl-SO_2-NR^{5a}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5a}R^{5b}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-; or

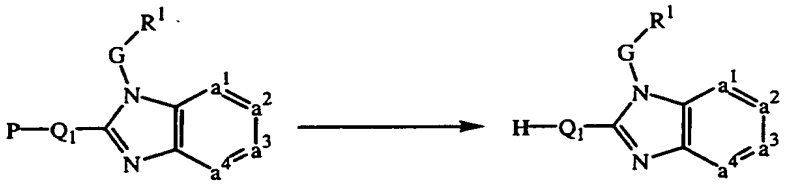
Q is a radical of formula (b-1); (b-2); (b-3); (b-4); (b-6); (b-7); (b-5) wherein v is 2; or (b-5) wherein v is 3, Y^1 is –CH(NR^2R^4)-, wherein X^2 is C(=O), and wherein R^1 is pyridyl or imidazolyl, each of said heterocycles substituted with 1 or where possible

more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)-aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5a}-, aryl-SO_2-NR^{5a}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5a}R^{5b}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-, or each of said heterocycles substituted with, where possible 2, 3 or 4 C_{1-6}alkyl groups; or wherein R^1 is pyrimidinyl or pyrazinyl, each of said heterocycles being substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)-aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5a}-, aryl-SO_2-NR^{5a}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5a}R^{5b}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-; or wherein R^1 is pyrrolyl or pyrazolyl, each of said heterocycles optionally being substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)-aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5a}-, aryl-SO_2-NR^{5a}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5a}R^{5b}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-.

In general, compounds of formula (I) can be prepared by reacting an intermediate of formula (II-a) or (II-b), wherein P represents a protecting group, such as, for example C_{1-4}alkyloxycarbonyl, or those protecting groups mentioned in Chapter 7 of 'Protective Groups in Organic Synthesis' by T Greene and P. Wuyts (John Wiley & Sons Inc., 1991), with an intermediate of formula (III), wherein W_1 is a suitable leaving group, such as a halo atom, e.g. chloro, bromo, in the presence of a suitable base, such as, e.g. sodium hydride, disodium carbonate. Said reaction can be performed in a reaction-inert solvent, such as *N,N*-dimethylformamide.



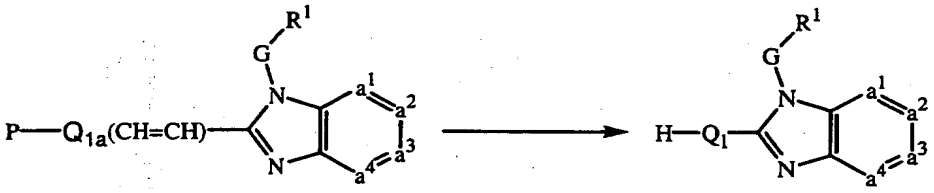
Compounds of formula (I) wherein, in the definition of Q, R^2 or R^6 is hydrogen, said Q being represented by H-Q_1, and said compounds being represented by formula (I-a), can be prepared by deprotecting an intermediate of formula (IV) wherein P represents a protecting group, for example C_{1-4}alkyloxycarbonyl, benzyl, or those protecting groups mentioned in Chapter 7 of 'Protective Groups in Organic Synthesis' by T Greene and P. Wuyts (John Wiley & Sons Inc., 1991).



When P represents, for example, C_{1-4}alkyloxycarbonyl, said deprotection reaction can be performed by, for example, acidic hydrolysis in the presence of a suitable acid, such as hydrobromic, hydrochloric, sulfuric, acetic, or trifluoroacetic acid or a mixture of said acids, or by alkaline hydrolysis in the presence of a suitable base, such as, for example potassium hydroxide, in a suitable solvent such as water, alcohol, a mixture of water-alcohol, methylene chloride. Suitable alcohols are methanol, ethanol, 2-propanol, 1-butanol and the like. In order to enhance the rate of the reaction, it is advantageous to heat the reaction mixture, in particular up to the reflux temperature. Alternatively, when P represents, for example, benzyl, the deprotection reaction can be performed by catalytic hydrogenation in the presence of hydrogen and an appropriate catalyst in a reaction-inert solvent. A suitable catalyst in the above reaction is, for example, platinum-on-charcoal, palladium-on-charcoal, and the like. An appropriate reaction-inert solvent for said reaction is, for example, an alcohol, e.g. methanol,

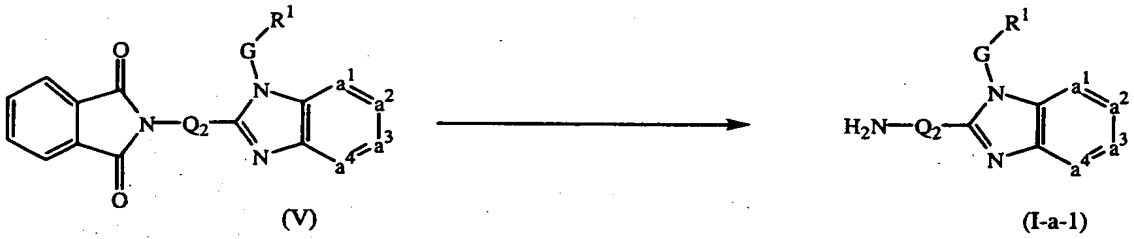
ethanol, 2-propanol and the like, an ester, e.g. ethylacetate and the like, an acid, e.g. acetic acid and the like.

The catalytic hydrogenation reaction described above can also be used to prepare a compound of formula (I-a) by deprotecting and reducing an intermediate of formula (IV) wherein Q_1 comprises an unsaturated bond, said Q_1 being represented by $Q_{1a}(CH=CH)$, and said intermediate being represented by formula (IV-a).



(IV-a) (I-a)

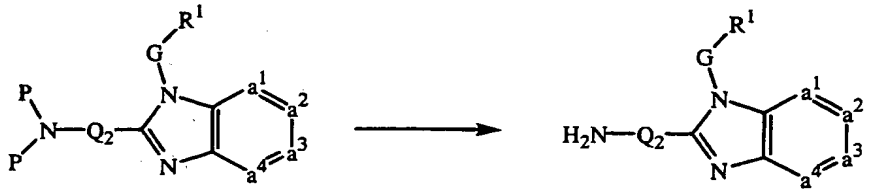
Compounds of formula (I) wherein, in the definition of Q, R^6 is hydrogen or R^2 and R^4 are both hydrogen, said Q being represented by H_2N-Q_2, and said compounds being represented by formula (I-a-1), can also be prepared by deprotecting an intermediate of formula (V).



(V) (I-a-1)

Said deprotection reaction can be performed in the presence of a suitable base such as, for example hydrazine, or in the presence of a suitable acid, such as hydrochloric acid and the like, in a suitable solvent, such as an alcohol, acetic acid and the like.

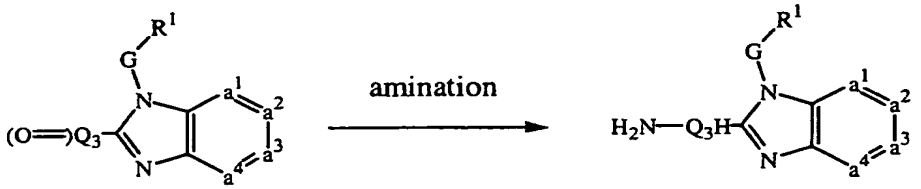
Compounds of formula (I-a-1) can also be prepared by deprotecting an intermediate of formula (VI) according to the procedure described for the preparation of compounds of formula (I-a).



(VI) (I-a-1)

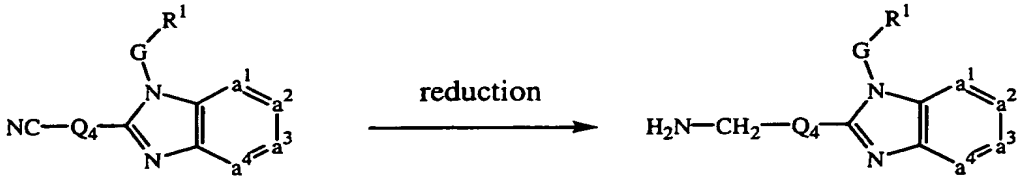
Alternatively, compounds of formula (I) wherein, in the definition of Q, R^6 is hydrogen or R^2 and R^4 are both hydrogen, and the carbon adjacent to the nitrogen carrying the R^6

or R^2 and R^4 substituents, contains at least one hydrogen, said Q being represented by H_2N-Q_3H, and said compounds being represented by formula (I-a-1-1) can also be obtained by reductive amination of intermediates of formula (VII) in the presence of a suitable amination reagent, such as, for example, ammonia, hydroxylamine, or benzylamine, and in the presence of a suitable reducing agent, e.g. hydrogen, and an appropriate catalyst. An appropriate catalyst in the above reaction is, for example, platinum-on-charcoal, palladium-on-charcoal, rhodium-on-Al_2O_3, and the like, optionally in the presence of a catalyst poison, such as a thiophene solution. A suitable reaction-inert solvent for the above reaction is, for example, an alcohol, e.g. methanol, ethanol, 2-propanol and the like.



(VII) (I-a-1-1)

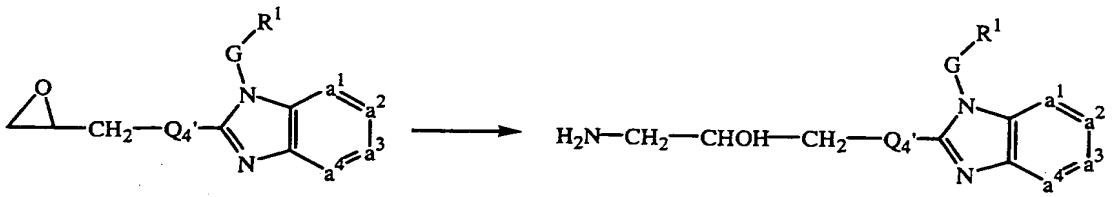
Compounds of formula (I), wherein Q comprises a $-CH_2NH_2$ moiety, said Q being represented by H_2N-CH_2-Q_4, and said compounds being represented by formula (I-a-1-2) can be prepared by reducing an intermediate of formula (VIII).



(VIII) (I-a-1-2)

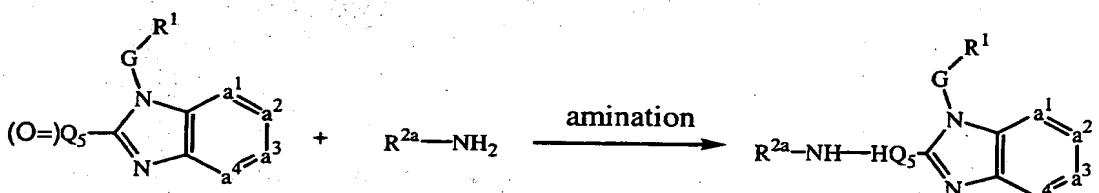
Said reduction can be performed with a suitable reducing agent, such as lithium aluminium hydride or hydrogen, optionally in the presence of a suitable catalyst, such as Raney Nickel. A suitable solvent for the above reaction is, for example, tetrahydrofuran, or a solution of ammonia in an alcohol. Suitable alcohols are methanol, ethanol, 2-propanol and the like.

Compounds of formula (I), wherein Q comprises a $-CH_2$–CHOH-CH_2-NH_2 moiety, said Q being represented by H_2N-CH_2-CHOH-CH_2-Q_4, and said compounds being represented by formula (I-a-1-2-1), can be prepared by reacting an intermediate of formula (LIV) with ammonia in the presence of a suitable reaction-inert solvent, such as an alcohol, e.g. methanol.



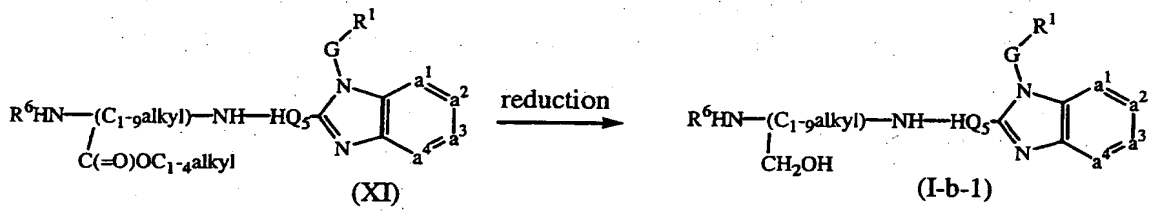
(LIV) (I-a-1-2-1)

Compounds of formula (I), wherein, in the definition of Q, R^2 is other than hydrogen, said R^2 being represented by R^{2a}, R^4 is hydrogen, and the carbon atom adjacent to the nitrogen atom carrying the R^2 and R^4 substituents, carries also at least one hydrogen atom, said Q being represented by R^{2a}-NH-HQ_5, and said compounds being represented by formula (I-b), can be prepared by reductive amination of an intermediate of formula (IX) with an intermediate of formula (X) in the presence of a suitable reducing agent, such as hydrogen, and a suitable catalyst, such as palladium-on-charcoal, platinum-on-charcoal, and the like. A suitable reaction-inert solvent for the above reaction is, for example, an alcohol, e.g. methanol, ethanol, 2-propanol and the like.



(IX) (X) (I-b)

Compounds of formula (I-b), wherein R^{2a} represents C_{1-10}alkyl substituted with NHR^6 and with hydroxy, and the carbon atom carrying the hydroxy, carries also two hydrogen atoms, said R^{2a} being represented by [(C_{1-9}alkyl)CH_2OH]-NHR^6, and said compounds being represented by formula (I-b-1), can be prepared by reducing an intermediate of formula (XI) in the presence of a suitable reducing agent, such as lithium aluminium hydride, in a suitable reaction-inert solvent, such as tetrahydrofuran.

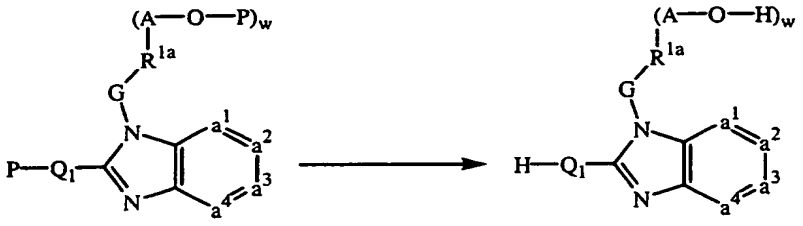


(XI) (I-b-1)

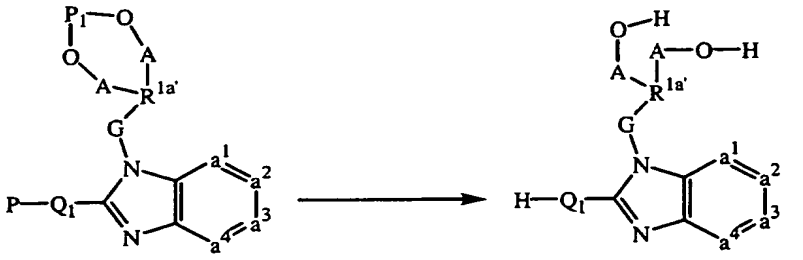
Compounds of formula (I) wherein, in the definition of Q, R^2 or R^6 is hydrogen, said Q being represented by H-Q_1, and wherein R^1 is a monocyclic heterocycle substituted with 1 or more substituents selected from hydroxy, hydroxyC_{1-6}alkyl, or $HO(-CH_2-CH_2-O)_n-$, said substituents being represented by formula A-OH, said R^1 being represented by R^{1a}-$(A\text{-}OH)_w$, with w being the amount of substituents on R^{1a}

ranging from 1 to 4, and said compounds being represented by formula (I-c), can be prepared by deprotecting an intermediate of formula (XII) with a suitable acid, such as hydrochloric acid and the like, optionally in the presence of a suitable solvent, such as an alcohol. Suitable alcohols are methanol, ethanol, 2-propanol and the like.

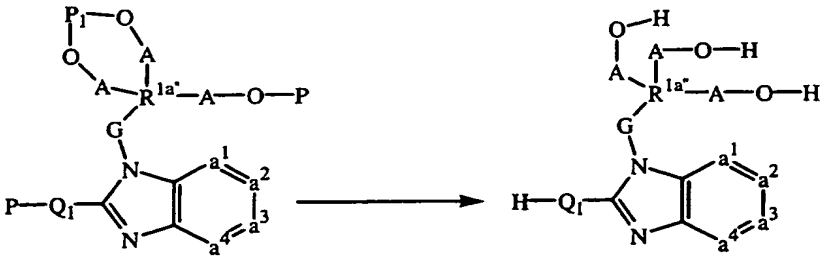
Alternatively, one protecting group may also protect more than one substituent of R^{1a}, said protecting group being represented by P_1, as represented by formula (XII-a). The two ways of protecting the substituents of R^{1a}, i.e. with a separate, as in formula (XII), or a combined, as in formula (XII-a), protecting group, may also be combined in the same intermediate, as represented by formula (XII-b).



(XII) (I-c)



(XII-a) (I-c-1)



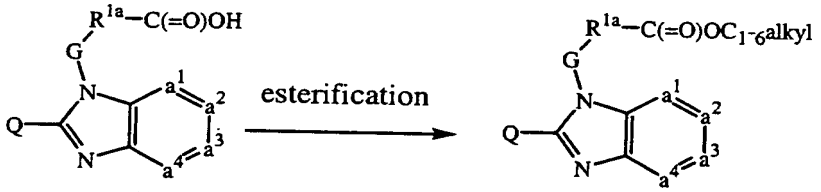
(XII-b) (I-c-2)

Compounds of formula (I) may be converted into each other following art-known functional group transformation reactions, comprising those described hereinafter.

The compounds of formula (I) may be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting

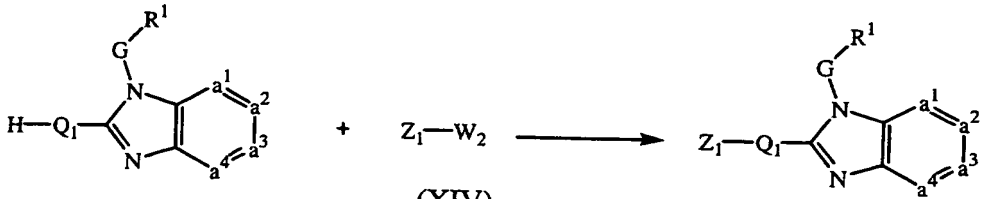
material of formula (I) with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxoalkanoic acids, e.g. peroxoacetic acid, alkylhydroperoxides, e.g. t.butyl hydro-peroxide. Suitable solvents are, for example, water, lower alcohols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

Compounds of formula (I), wherein R^1 is monocyclic heterocycle substituted with C_{1-6}alkyloxycarbonyl, said R^1 being represented by R^{1a}-C(=O)OC_{1-6}alkyl, and said compounds being represented by formula (I-d), can be prepared by esterification of a compound of formula (XIII) in the presence of a suitable alcohol, e.g. methanol, ethanol, propanol, butanol, pentanol, hexanol and the like, and in the presence of a suitable acid, such as hydrochloric acid and the like.



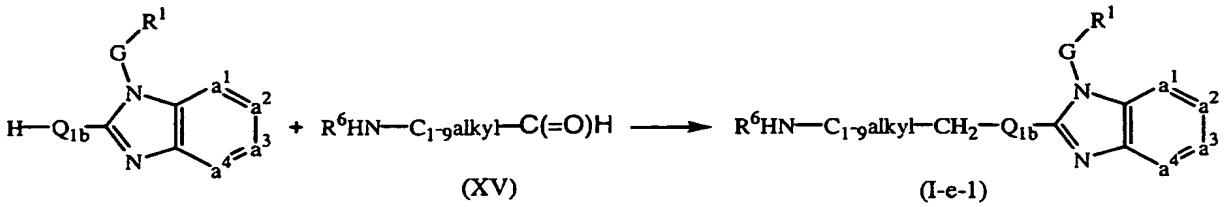
(XIII) (I-d)

Compounds of formula (I-a) may be converted into compounds of formula (I) wherein, in the definition of Q, R^2 or R^6 are other than hydrogen, said R^2 or R^6 being represented by Z_1, said Q being represented by Z_1-Q_1, and said compounds being represented by formula (I-e), by reaction with a reagent of formula (XIV), wherein W_2 is a suitable leaving group, such as a halo atom, e.g. bromo, or 4-methylbenzenesulphonate, in the presence of a suitable base, such as, for example disodium carbonate, dipotassium carbonate, sodium hydroxide and the like, in a reaction-inert solvent, e.g. 3-methyl-2-butanone, acetonitrile, *N*,*N*-dimethylformamide.



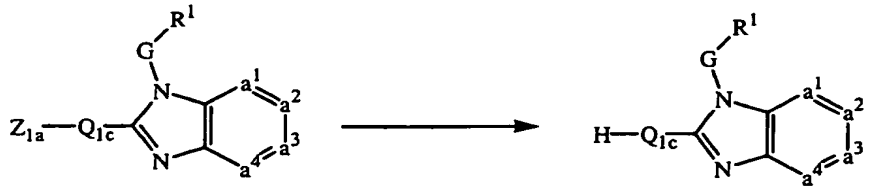
(I-a) (XIV) (I-e)

Compounds of formula (I-e), wherein, in the definition of Z_1, R^2 is CH_2-C_{1-9}alkyl substituted with NHR^6, said compounds being represented by formula (I-e-1), can also be prepared by reacting a compound of formula (I-a) wherein, in the definition of H-Q_1, R^2 is hydrogen, said H-Q_1 being represented by H-Q_{1b}, and said compounds being represented by formula (I-a-2), with an intermediate of formula (XV), in the presence of a suitable reducing agent, such as sodium cyanoborohydride, in a suitable reaction-inert solvent, such as an alcohol.



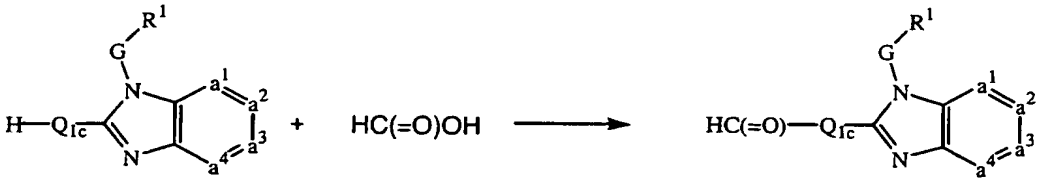
(I-a-2) (XV) (I-e-1)

Compounds of formula (I-e), wherein Z_1 comprises formyl, C_{1-6}alkylcarbonyl or C_{1-6}alkyloxycarbonyl, said Z_1 being represented by Z_{1a}, and said compounds being represented by formula (I-e-2), can be converted into compounds of formula (I-a) wherein, in the definition of H-Q_1, R^6 is hydrogen, said H-Q_1 being represented by H-Q_{1c}, and said compounds being represented by formula (I-a-3), by acidic hydrolysis in the presence of a suitable acid, such as hydrobromic, hydrochloric, sulfuric, acetic, or trifluoroacetic acid or a mixture of said acids, or by alkaline hydrolysis in the presence of a suitable base, such as, for example potassium hydroxide, in a suitable solvent such as water, alcohol, a mixture of water-alcohol, methylene chloride. Suitable alcohols are methanol, ethanol, 2-propanol, 1-butanol, sec. butanol and the like. In order to enhance the rate of the reaction, it is advantageous to work at elevated temperatures.



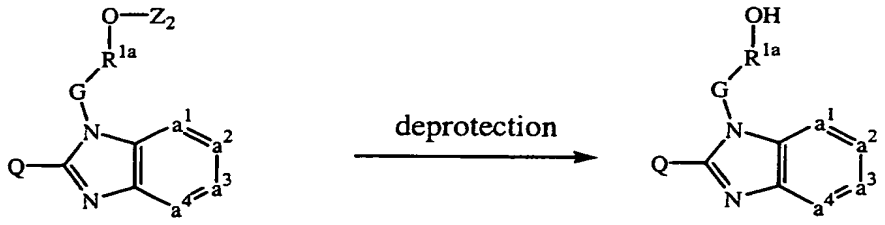
(I-e-2) (I-a-3)

Compounds of formula (I-e-2) wherein Z_{1a} comprises formyl, said compounds being represented by formula (I-e-2-1), can be prepared by reacting a compound of formula (I-a-3) with formic acid.



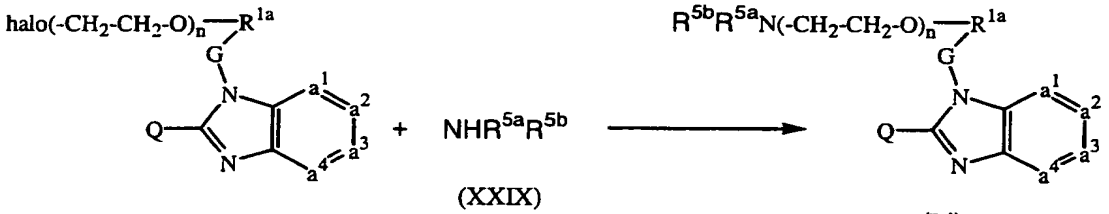
(I-a-3) (I-e-2-1)

Compounds of formula (I) wherein R^1 is monocyclic heterocycle substituted with hydroxy, said R^1 being represented by HO-R^{1a}, and said compounds being represented by formula (I-f), can be prepared by deprotecting a compound of formula (I-g), wherein R^1 is monocyclic heterocycle substituted with C_{1-6}alkyloxy or arylC_{1-6}alkyloxy, said C_{1-6}alkyl or arylC_{1-6}alkyl being represented by Z_2, and said R^1 being represented by Z_2-O-R^{1a}. Said deprotection can be performed in a reaction-inert solvent, such as, for example methylene chloride, in the presence of a suitable deprotecting agent, e.g. tribromoborane.



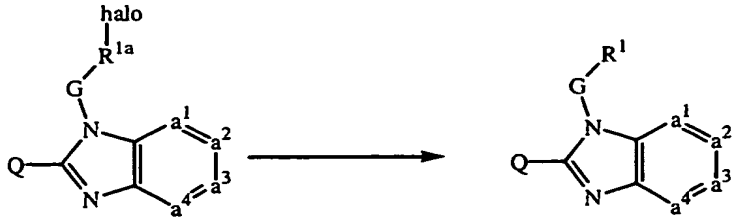
(I-g) (I-f)

Compounds of formula (I) wherein R^1 is monocyclic heterocycle substituted with halo(-CH_2-CH_2-O)$_n$, said compounds being represented by formula (I-h), can be converted into compounds of formula (I-i) by reaction with the appropriate amine of formula (XXIX) in a suitable reaction-inert solvent, e.g. tetrahydrofuran.



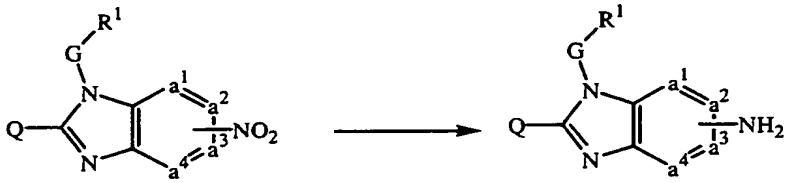
(I-h) (XXIX) (I-i)

Compounds of formula (I) wherein R^1 is monocyclic heterocycle substituted with halo, said compounds being represented by formula (I-j) can be converted into compounds of formula (I) by reaction with 1-butanethiol in the presence of palladium-on-charcoal and CaO in a suitable reaction-inert solvent, such as tetrahydrofuran.



(I-j) (I)

Compounds of formula (I) wherein a hydrogen atom in the radicals of formula (a-1), (a-2), (a-3), (a-4) or (a-5) is replaced by nitro, said compounds being represented by formula (I-k) may be reduced to a compound of formula (I-l) in the presence of a suitable reducing agent, such as hydrogen, in the presence of a suitable catalyst, such as platinum-on-charcoal, and optionally in the presence of a suitable catalyst poison, e.g. a thiophene solution. The reaction may be performed in a suitable reaction-inert solvent, such as an alcohol.

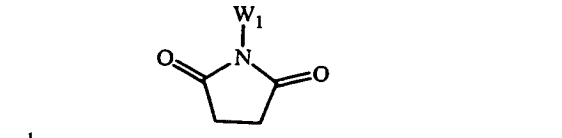


(I-k) (I-l)

In the following paragraphs, there are described several methods of preparing the intermediates in the foregoing preparations. A number of intermediates and starting materials are commercially available or are known compounds which may be prepared according to conventional reaction procedures generally known in the art or analogous to the procedures described in EP-A-0005318, EP-A-0099139, EP-A-0151824 , EP-A-0151826 , EP-A-0232937 , EP-A-0295742 , EP-A-0297661 , EP-A-0539420 , EP-A-0539421 , US 4,634,704 , US 4,695,569.

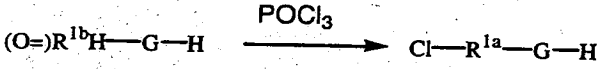
In the foregoing and the following preparations, the reaction mixture is worked up following art-known methods and the reaction product is isolated and, if necessary, further purified.

Intermediates of formula (III) can be prepared by reacting an intermediate of formula (XVI) with a suitable leaving group, i.e. W_1, introducing agent, e.g. 1-halo, 2,5-pyrrolidinedione, in the presence of dibenzoyl peroxide, in a reaction-inert solvent, e.g. tetrachloromethane.



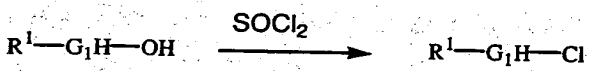
(XVI) (III)

Intermediates of formula (XVI), wherein R^1 is monocyclic heterocycle substituted with chloro, said R^1 being represented by Cl-R^{1a} and said intermediates being represented by formula (XVI-a), can be prepared by reacting an intermediate of formula (XVII), wherein (O=)R^{1b}H is defined as a carbonyl derivative of R^{1a} wherein one carbon or nitrogen, adjacent to the carbonyl, carries at least one hydrogen, with phosphorus oxychloride. Intermediates of formula (XVII) may also react as their enol tautomeric forms.



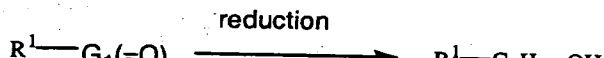
(XVII) (XVI-a)

Intermediates of formula (III) wherein W_1 is chloro, which is attached to a carbon atom carrying at least one hydrogen, said G being represented by G_1H, and said intermediates being represented by formula (III-a), can also be prepared by reacting an intermediate of formula (XVIII) with thionylchloride in a reaction-inert solvent, e.g. methylenechloride.



(XVIII) (III-a)

Intermediates of formula (XVIII) can be prepared by reducing an intermediate of formula (XIX) in a reaction-inert solvent, e.g. an alcohol, in the presence of a suitable reducing agent, e.g. sodium borohydride.

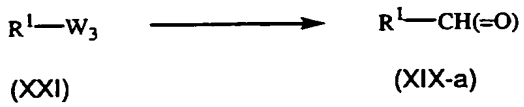


(XIX) (XVIII)

Alternatively, intermediates of formula (XVIII) can also be prepared by deprotecting an intermediate of formula (XX), wherein P is a suitable protecting group, e.g. C_{1-4}alkylcarbonyl, in a reaction-inert solvent, such as an alcohol, in the presence of a suitable base, e.g. sodium hydroxide.

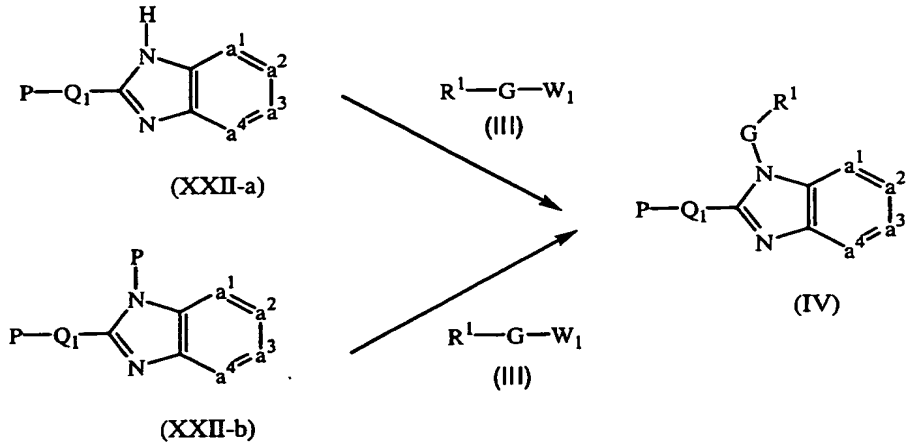
(XX) (XVIII)

Intermediates of formula (XIX), wherein $G_1(=O)$ is $CH(=O)$, said intermediates being represented by formula (XIX-a), can be prepared by reacting an intermediate of formula (XXI), wherein W_3 is a suitable leaving group, such as a halo atom, e.g. bromo, with *N,N*-dimethylformamide in the presence of butyllithium in a reaction-inert solvent, e.g. tetrahydrofuran, diethylether or a mixture thereof.



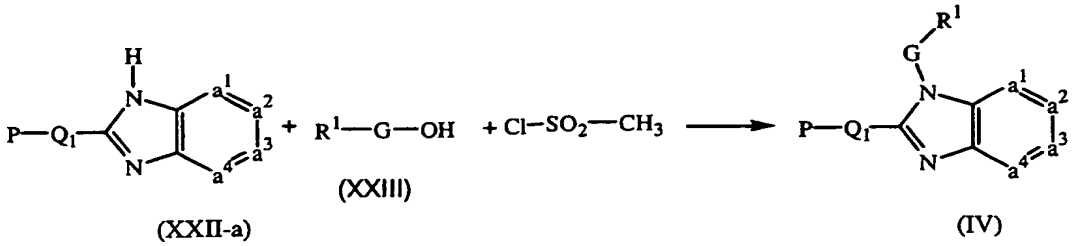
(XXI) (XIX-a)

Intermediates of formula (IV) can be prepared by reacting an intermediate of formula (XXII-a) or (XXII-b), wherein P represents a suitable protecting group, such as, for example, C_{1-4}alkyloxycarbonyl, with an intermediate of formula (III) according to the reaction described for the general preparation of compounds of formula (I).



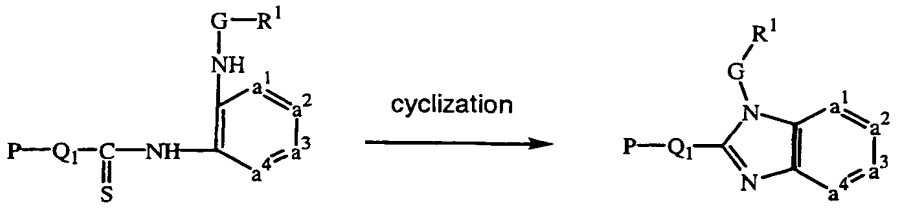
(XXII-a) (XXII-b) (III) (III) (IV)

Intermediates of formula (IV) can also be prepared by reacting an intermediate of formula (XXII-a) with an intermediate of formula (XXIII) that has reacted with methanesulfonyl chloride, in the presence of a suitable base, such as sodium hydride, and in the presence of a suitable reaction-inert solvent, e.g. *N,N*-dimethylformamide.



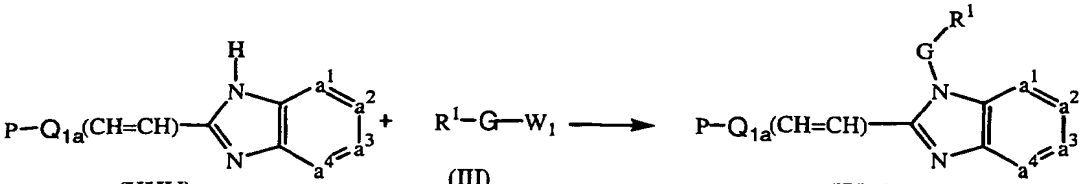
(XXII-a) (XXIII) (IV)

Intermediates of formula (IV) can also be prepared by a cyclization reaction of an intermediate of formula (XXIV) in a reaction-inert solvent, e.g. an alcohol or *N,N*-dimethylformamide, in the presence of mercury oxide and sulphur.



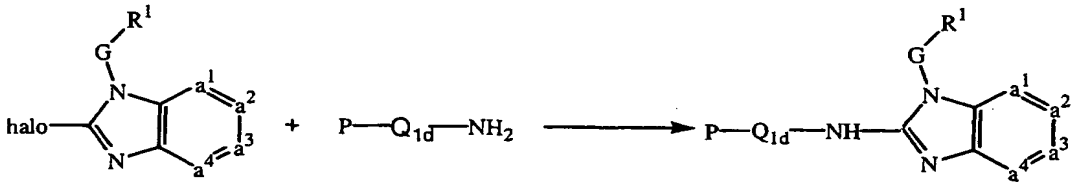
(XXIV) (IV)

Intermediates of formula (IV) wherein Q_1 comprises an unsaturated bond, said Q_1 being represented by Q_{1a}(CH=CH), and said intermediates by formula (IV-a), can be prepared by reacting an intermediate of formula (XXV) with an intermediate of formula (III) in the presence of a suitable base, such as dipotassium carbonate.



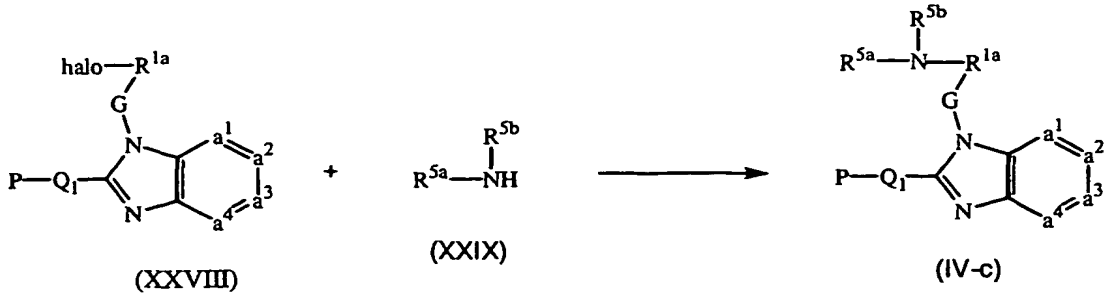
(XXV) (III) (IV-a)

Intermediates of formula (IV) wherein, in the definition of Q_1, the X^1 moiety of formula (b-1), (b-2) or (b-3) represents NH, or the Y^2 moiety of formula (b-4) or (b-5) represents CH-NH, said Q_1 being represented by Q_{1d}-NH, and said intermediates by formula (IV-b), may also be prepared by reacting an intermediate of formula (XXVI) with an intermediate of formula (XXVII).



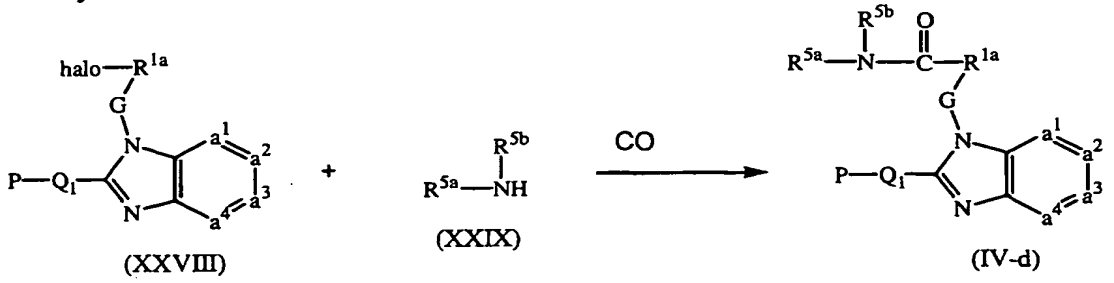
(XXVI) (XXVII) (IV-b)

Intermediates of formula (IV) wherein R^1 is monocyclic heterocycle substituted with amino or mono- or di(C_{1-6}alkyl)amino, said R^1 being represented by $R^{5a}R^{5b}N$-R^{1a}, wherein R^{5a} and R^{5b} are defined as described hereinabove, and said intermediates being represented by formula (IV-c), can be prepared by reacting an intermediate of formula (XXVIII) with an appropriate amine, represented by formula (XXIX), in the presence of an appropriate catalyst, e.g. palladium, and (R)-(+)-2,2'-bis(diphenyl-phosphino)-1,1'-binaphtyl, in a suitable reaction-inert solvent, e.g. tetrahydrofuran.



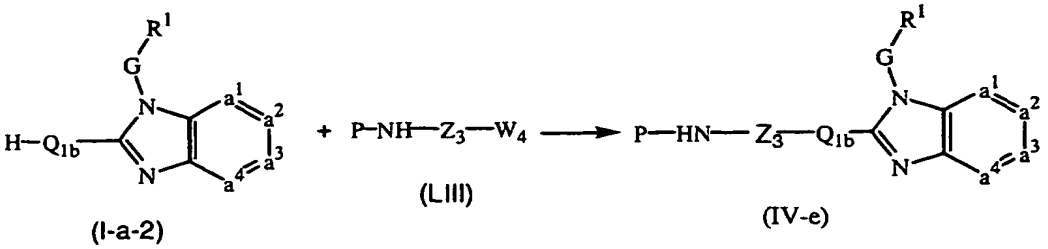
(XXVIII) (XXIX) (IV-c)

Intermediates of formula (IV) wherein R^1 is monocyclic heterocycle substituted with C(=O)-$NR^{5a}R^{5b}$, wherein R^{5a} and R^{5b} are defined as described hereinabove, said R^1 being represented by $R^{5a}R^{5b}N$-C(=O)-R^{1a}, and said intermediates being represented by formula (IV-d), can be prepared by reacting an intermediate of formula (XXVIII) with an appropriate amine, represented by formula (XXIX), under an atmosphere of carbon monoxide, in the presence of a suitable catalyst, e.g. palladium (II) acetate, and 1,3-bis(diphenylphosphino)propane, in a suitable reaction-inert solvent, e.g. tetrahydrofuran.



(XXVIII) (XXIX) (IV-d)

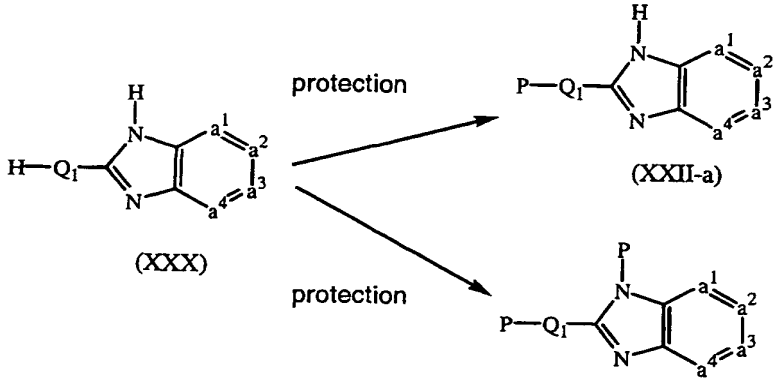
Intermediates of formula (IV) wherein P-Q_1 comprises C_{1-10}alkyl or C_{3-7}cycloalkyl substituted with NH-P, said C_{1-10}alkyl or C_{3-7}cycloalkyl being represented by Z_3, said P-Q_1 being represented by P-NH-Z_3-Q_{1b}, and said intermediates being represented by formula (IV-e), can be prepared by reacting a compound of formula (I-a-2) with an intermediate of formula (LIII), wherein W_4 represents a suitable leaving group, such as p-toluenesulphonate. Said reaction can be performed in a reaction-inert solvent, e.g. acetonitrile, in the presence of a suitable base, e.g. dipotassium carbonate.



(I-a-2) (LIII) (IV-e)

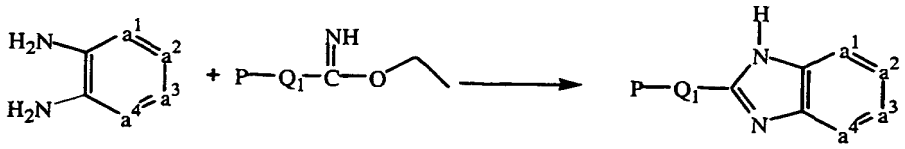
Intermediates of formula (XXII-a) or (XXII-b) can be prepared by protecting an intermediate of formula (XXX) with a suitable protecting group, such as, for example,

C_{1-4}alkyloxycarbonyl, in a reaction-inert solvent, such as methylene chloride or an alcohol, e.g. methanol, ethanol, 2-propanol and the like, in the presence of a suitable reagent, e.g. diC_{1-4}alkyldicarbonate, and optionally in the presence of a suitable base, e.g. sodium acetate.



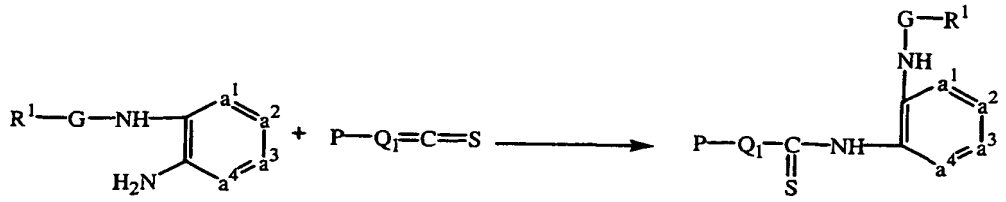
(XXX) (XXII-a) (XXII-b)

Intermediates of formula (XXII-a) can also be prepared by reacting an intermediate of formula (XXXI) with P-Q_1-C(=NH)-O-CH_2-CH_3 in a reaction-inert solvent, such as an alcohol.



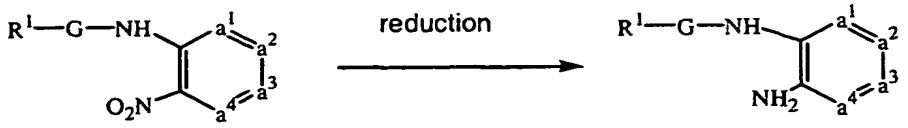
(XXXI) (XXII-a)

Intermediates of formula (XXIV) can be prepared by reacting an intermediate of formula (XXXII) with an intermediate of formula P-Q_1=C=S, which is synthesized according to the procedures described in EP 0005318, in a reaction-inert solvent, such as an alcohol, e.g. ethanol. To increase the reaction rate, the reaction may be performed at elevated temperatures.



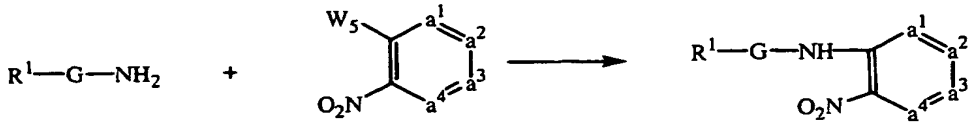
(XXXII) (XXIV)

Intermediates of formula (XXXII) can be obtained by reducing an intermediate of formula (XXXIII) in a reaction-inert solvent, e.g. an alcohol, in the presence of a suitable reducing agent, e.g. hydrogen, and an appropriate catalyst, e.g. Raney Nickel.



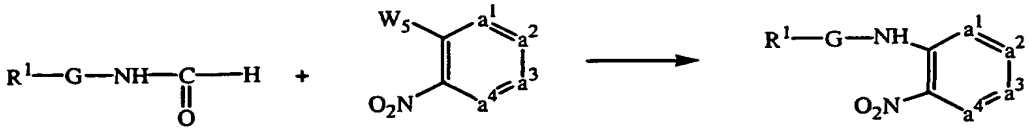
(XXXIII) (XXXII)

Intermediates of formula (XXXIII) can be prepared by reacting an intermediate of formula(XXXIV) with an intermediate of formula (XXXV), in which W_5 represents a suitable leaving group, such as a halo atom, e.g. chloro. The reaction may be performed in a reaction-inert solvent, e.g. acetonitrile, in the presence of a suitable base, e.g. dipotassium carbonate.



(XXXIV) (XXXV) (XXXIII)

Intermediates of formula (XXXIII) can also be prepared by reacting an intermediate of formula (XXXV) with an intermediate of formula (XXXVI) (J. Org. Chem., 25, p 1138, 1960) in a reaction-inert solvent, e.g. *N,N*-dimethylformamide, in the presence of an appropriate base, e.g. sodium hydride.

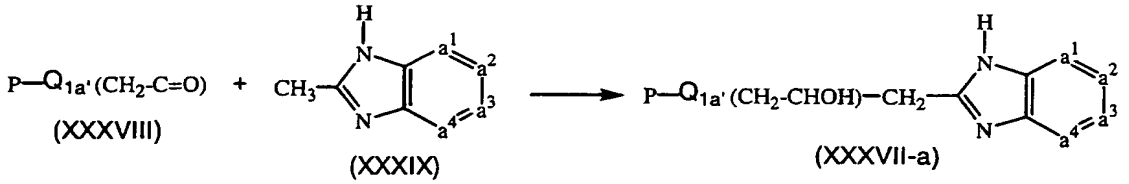


(XXXVI) (XXXV) (XXXIII)

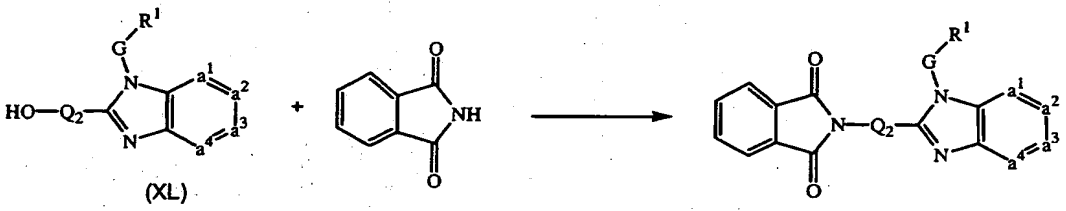
Intermediates of formula (XXV) can be prepared by dehydrating an intermediate of formula (XXXVII) with a suitable acid, such as sulfuric acid.

(XXXVII) (XXV)

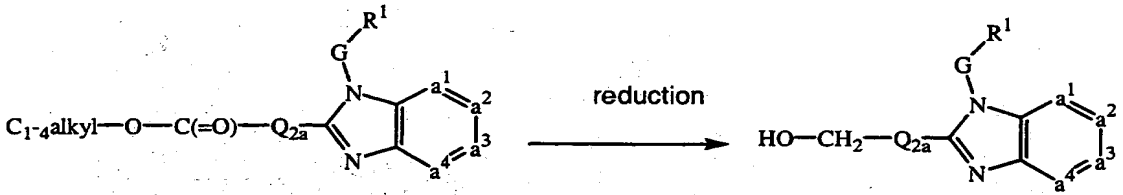
Intermediates of formula (XXXVII) wherein, in the definition of Q_{1a}, X^1 or X^2 is CH_2, said Q_{1a} being represented by $Q_{1a'}$, and said intermediates being represented by formula (XXXVII-a), can be prepared by reacting a carbonyl moiety of formula (XXXVIII) with an intermediate of formula (XXXIX) in the presence of *N,N*-diisopropylamine and butyl lithium, in a suitable reaction-inert solvent, e.g. tetrahydrofuran.



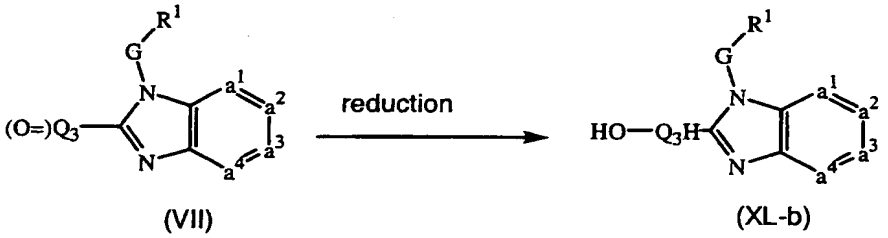
Intermediates of formula (V) can be prepared by reacting an intermediate of formula (XL) with 1*H*-isoindole-1,3 (2*H*)-dione in the presence of triphenylphosphine and diethyl azodicarboxylate.



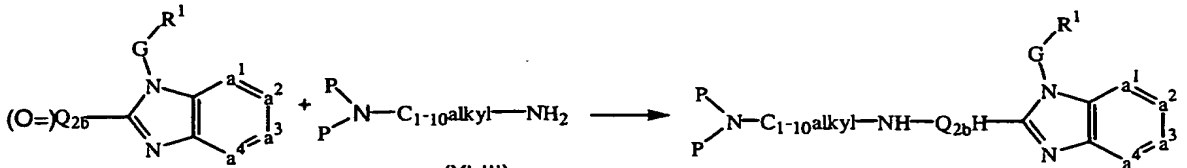
Intermediates of formula (XL) wherein, in the definition of Q_2, the carbon atom carrying the hydroxy, also carries two hydrogen atoms, said HO-Q_2 being represented by HO-CH_2-Q_{2a}, and said intermediates being represented by formula (XL-a), can be prepared by reducing an intermediate of formula (XLI) in the presence of a suitable reducing agent, such as lithium aluminium hydride, in a suitable reaction-inert solvent, e.g. tetrahydrofuran.



Intermediates of formula (XL), wherein, in the definition of Q_2, the carbon atom carrying the hydroxy, carries also at least one hydrogen, said HO-Q_2 being represented by HO-Q_3H, and said intermediates being represented by formula (XL-b), can be prepared by reducing an intermediate of formula (VII) with a suitable reducing agent, e.g. sodium borohydride, in a reaction-inert solvent, e.g. an alcohol.

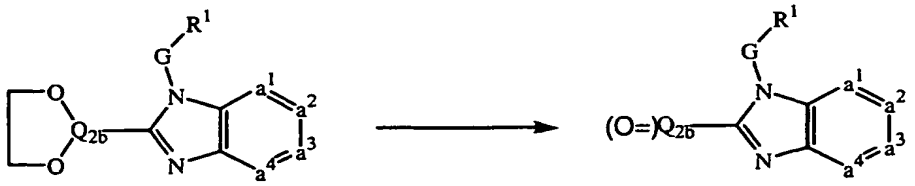


Intermediates of formula (VI) wherein, in the definition of Q_2, R^2 is C_{1-10}alkyl substituted with $N(P)_2$ and the carbon atom adjacent to the nitrogen atom carrying the R^2 substituent carries also at least one hydrogen atom, said Q_2 being represented by $(P)_2$-N-C_{1-10}alkyl-NH-$Q_{2b}H$, and said intermediates being represented by formula (VI-a), can be prepared by reductive amination of an intermediate of formula (XLII) with an intermediate of formula (XLIII) in the presence of a suitable reductive agent, such as hydrogen, and a suitable catalyst, such as palladium-on-charcoal, platinum-on-charcoal, and the like, and optionally in the presence of a suitable catalyst poison, such as a thiophene solution. A suitable solvent in this reaction is a reaction-inert solvent, such as an alcohol.



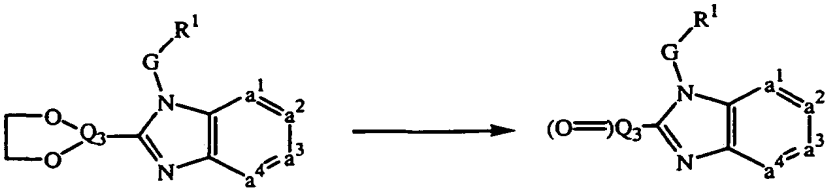
(XLII) (XLIII) (VI-a)

Intermediates of formula (XLII) can be prepared by deprotecting an intermediate of formula (XLIV) in the presence of a suitable acid, such as hydrochloric acid and the like, in a suitable solvent, e.g. water.



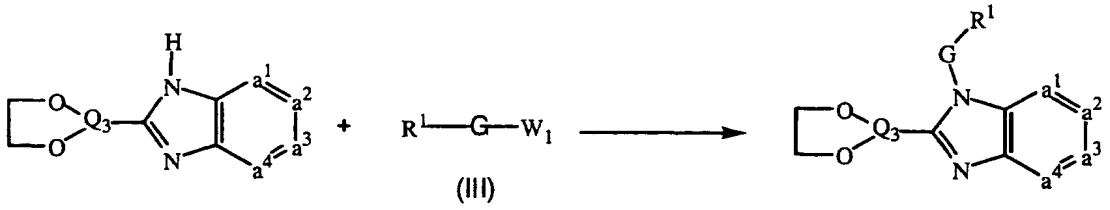
(XLIV) (XLII)

Intermediates of formula (VII) may be prepared by deprotecting an intermediate of formula (XLV) in the presence of a suitable acid, e.g. hydrochloric acid and the like.



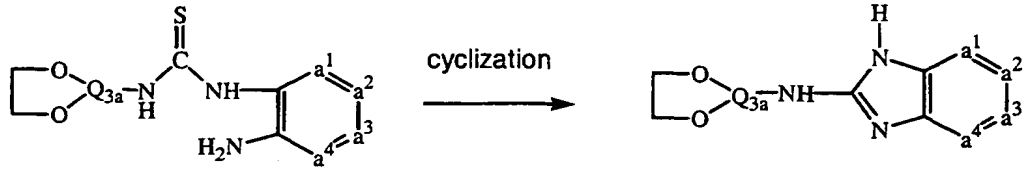
(XLV) (VII)

Intermediates of formula (XLV) can be prepared by reacting an intermediate of formula (XLVI) with an intermediate of formula (III) in the presence of a suitable base, e.g. dipotassium carbonate, in a suitable reaction-inert solvent, e.g. acetonitrile.



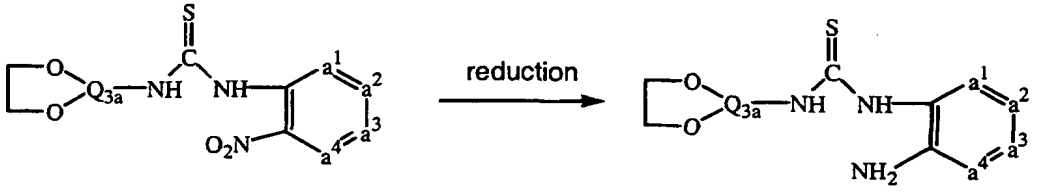
(XLVI) (III) (XLV)

Intermediates of formula (XLVI) wherein, in the definition of Q_3, the X^1 moiety of formula (b-1), (b-2) or (b-3) represents NH, or the Y^2 moiety of formula (b-4) or (b-5) represents CH-NH, said Q_3 being represented by Q_{3a}-NH, and said intermediates being represented by formula (XLVI-a), may be prepared by cyclizing an intermediate of formula (XLVII) in the presence of mercury oxide and sulphur, in a suitable reaction-inert solvent, e.g. an alcohol.



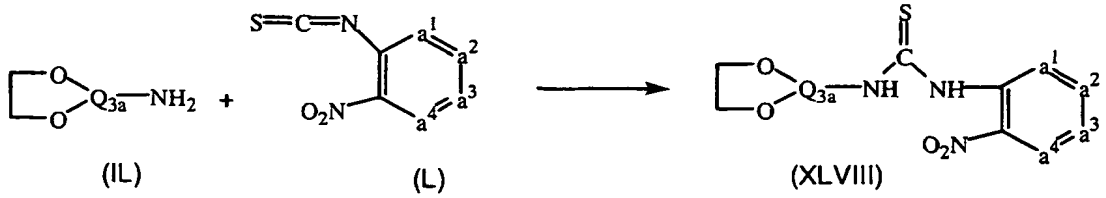
(XLVII) (XLVI-a)

Intermediates of formula (XLVII) can be prepared by reducing an intermediate of formula (XLVIII) in the presence of a suitable reducing agent, such as hydrogen, in the presence of a suitable catalyst, such as palladium-on-charcoal, platinum-on-charcoal and the like, in a suitable solvent, e.g. a mixture of ammonia in alcohol. Suitable alcohols are methanol, ethanol, 2-propanol and the like.



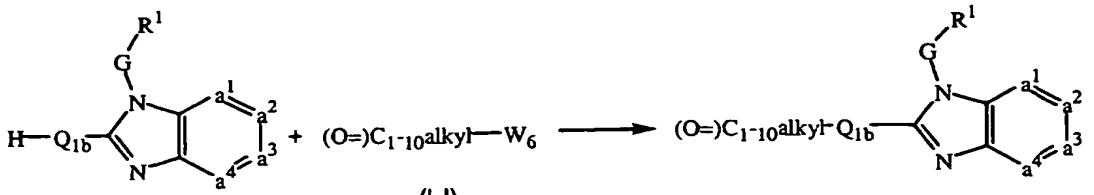
(XLVIII) (XLVII)

Intermediates of formula (XLVIII) can be prepared by reacting an intermediate of formula (IL) with an intermediate of formula (L) in a suitable reaction-inert solvent, e.g. ethanol.



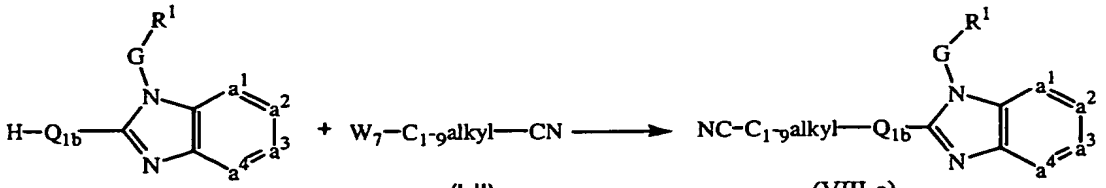
(IL) (L) (XLVIII)

Intermediates of formula (VII), wherein, in the definition of Q_3, R^2 comprises C_{1-10}alkyl, said Q_3 being represented by C_{1-10}alkylQ_{1b}, and said intermediates being represented by formula (VII-a), can be prepared by reacting a compound of formula (I-a-2) with a reagent of formula (LI), wherein (O=)C_{1-10}alkyl represents a carbonyl derivative of C_{1-10}alkyl and wherein W_6 is a suitable leaving group, such as a halo atom, e.g. bromo, in a reaction-inert solvent, e.g. acetonitrile, in the presence of a suitable base, e.g. dipotassium carbonate.



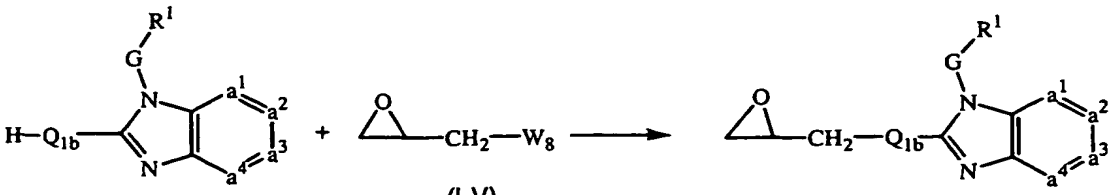
(I-a-2) (LI) (VII-a)

Intermediates of formula (VIII) wherein Q_4 comprises C_{1-9}alkyl, said Q_4 being represented by C_{1-9}alkyl-Q_{1b}, and said intermediates being represented by formula (VIII-a), can be prepared by reacting a compound of formula (I-a-2) with a reagent of formula (LII), wherein W_7 represents a suitable leaving group, such as a halo atom, e.g. chloro, in a reaction-inert solvent, e.g. 3-methyl-2-butanone, in the presence of a suitable base, e.g. dipotassium carbonate, sodium bicarbonate and the like.



(I-a-2) (LII) (VIII-a)

Intermediates of formula (LIV), wherein Q_4, represents Q_{1b}, said intermediates being represented by formula (LIV-a), can be prepared by reacting a compound of formula (I-a-2) with an intermediate of formula (LV), wherein W_8 represents a suitable leaving group, such as a halo atom, e.g. chloro, in the presence of a suitable base, such as disodium carbonate, and in the presence of a suitable solvent, such as 3-methyl-2-butanone.



(I-a-2) (LV) (LIV-a)

The compounds of formula (I), or any subgroup thereof, show antiviral properties. Viral infections treatable using the compounds and methods of the present invention include those infections brought on by ortho- and paramyxoviruses and in particular by human and bovine respiratory syncytial virus (RSV).

The *in vitro* antiviral activity against RSV of the present compounds was tested in a test as described in the experimental part of the description, and may also be demonstrated in a virus yield reduction assay. The *in vivo* antiviral activity against RSV of the present compounds may be demonstrated in a test model using cotton rats as described in Wyde et al. (Antiviral Research (1998), 38, 31-42).

Due to their antiviral properties, particularly their anti-RSV properties, the compounds of formula (I) or any subgroup thereof, their prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms, are useful in the treatment of individuals experiencing a viral infection, particularly a RSV infection, and for the prophylaxis of these infections. In general, the compounds of the present invention may be useful in the treatment of warm-blooded animals infected with viruses, in particular the respiratory syncytial virus.

The compounds of the present invention or any subgroup thereof may therefore be used as medicines. Said use as a medicine or method of treatment comprises the systemic administration to viral infected subjects of an amount effective to combat the conditions associated with the viral infection.

The compounds of the present invention or any subgroup thereof may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in addition salt form or as metal complex, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, particularly, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders,

disintegrating agents and the like in the case of powders, pills, capsules, and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin. The compounds of the present invention may also preferably be administered via inhalation.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, powder packets, suppositories, wafers, injectable solutions or suspensions and the like, and segregated multiples thereof.

It may be appropriate to administer an antivirally effective daily dosage as two, three, four or more sub-doses at appropriate intervals throughout the day. Said sub-doses may be formulated as unit dosage forms.

The exact dosage and frequency of administration depends on the particular compound of formula (I) used, the particular condition being treated, the severity of the condition being treated, the age, weight, sex, extent of disorder and general physical condition of the particular patient as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that said effective daily amount may be lowered or increased depending on the response of the treated

subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention.

Also, the combination of another antiviral agent and a compound of formula (I) can be used as a medicine. Thus, the present invention also relates to a product containing (a) a compound of formula (I), and (b) another antiviral compound, as a combined preparation for simultaneous, separate or sequential use in antiviral treatment. The different drugs may be combined in a single preparation together with pharmaceutically acceptable carriers.

The following examples are intended to illustrate the present invention.

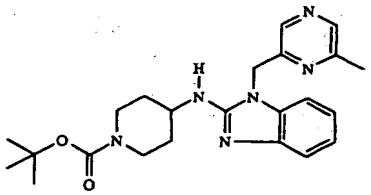
Experimental part

Hereinafter, "DMF" is defined as *N,N*-dimethylformamide, "DIPE" is defined as diisopropylether, "DMSO" is defined as dimethylsulfoxide, and "THF" is defined as tetrahydrofuran.

Preparation of the intermediate compounds

Example A1

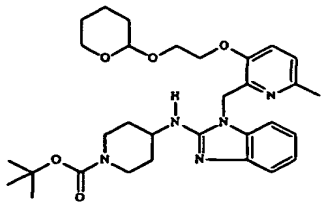
a) $NaOCH_3$ (0.2 mol) was added to a mixture of *N*-(4-piperidinyl)-1*H*-benzimidazol-2-amine dihydrobromide (0.1 mol) in methanol (389ml), the mixture was cooled on an ice bath and stirred for 2 hours. Bis(1,1-dimethylethyl) dicarbonoate (0.1mol) was added to a cooled mixture on an ice bath and then stirred for 18 hours at room temperature. The mixture was evaporated and suspended in water/DIPE. The residue was filtered off, washed with water/DIPE and dried. The residue was boiled up in CH_3OH. Yield : 17.46g of 1,1-dimethylethyl 4-(1*H*-benzimidazol-2-ylamino)-1-piperidinecarboxylate (55.2%) (interm. 1).

b) Preparation of  (interm. 2)

1-Bromo-2,5-pyrrolidinedione (0.055 mol) and then dibenzoyl peroxide (cat.quant.) were added to a mixture of 2,6-dimethylpyrazine (0.05 mol) in CCl_4 (100ml). The mixture was stirred and refluxed for 4 hours, stirred at room temperature under N_2 flow overnight, cooled on an ice bath and filtered. The filtrate was evaporated, to give residue 1. NaH (0.04 mol) was added to a solution of intermediate (1) (0.04 mol) in DMF (150ml). The mixture was stirred at room temperature under N_2 flow for 1 hour. Residue 1 was dissolved in DMF (50ml) and added dropwise to the mixture. The mixture was stirred at 50°C overnight. DMF was evaporated. The residue was taken

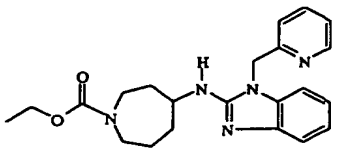
up in H_2O and the mixture was extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2). The pure fractions were collected and the solvent was evaporated. Yield: 6.82g of intermediate (2) (32%).

Example A2

Preparation of  (interm. 3)

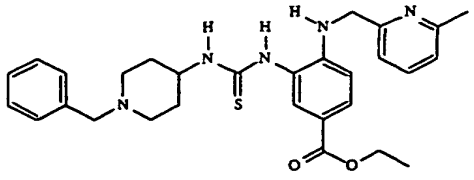
Reaction under N_2 flow. NaH 60% (0.02 mol) was added to a mixture of (±)-6-methyl-3-[2-[(tetrahydro-2*H*-pyran-2-yl)oxy]ethoxy]-2-pyridinemethanol (0.02 mol) in DMF (75ml). Methanesulfonyl chloride (0.02 mol) was added. The mixture was added at room temperature to a mixture of intermediate (1) (0.02 mol) and NaH (0.022 mol) in DMF (100ml), previously stirred at 40°C for 1 hour. The mixture was stirred at room temperature overnight. The solvent was evaporated. The residue was taken up in H_2O and CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/ (CH_3OH/NH_3) 97/3). The pure fractions were collected and the solvent was evaporated. Yield: 3.52g of intermediate (3) (31%).

Example A3

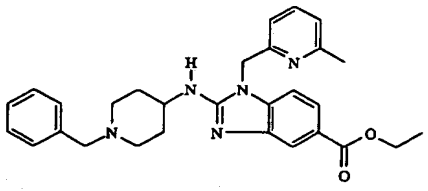
Preparation of  (interm. 4)

2-Chloro-1-(2-pyridylmethyl)-1*H*-benzimidazole (0.0615 mol) and ethyl 4-amino-hexahydro-1*H*-azepine-1-carboxylate (0.123 mol) were stirred at 160°C for 3 hours. H_2O was added and the mixture was extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue (13.6g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 98/2/0.1). The pure fractions were collected and the solvent was evaporated. Yield: 10.5g of intermediate (4) (43%).

Example A4

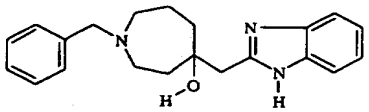
a) Preparation of  (interm. 5)

A mixture of ethyl 3-amino-4-[[(6-methyl-2-pyridyl)methyl]amino]benzoate (0.166 mol) and 4-isothiocyanato-1-(phenylmethyl)piperidine (0.166 mol) in ethanol (500ml) was stirred and refluxed for 8 hours and at room temperature overnight. The precipitate was filtered off and used without further purification. Yield: intermediate (5).

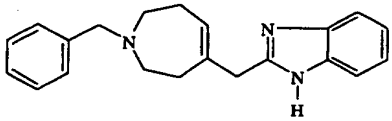
b) Preparation of  (interm. 6)

A mixture of intermediate (5) (0.16 mol), HgO (0.192 mol) and S (spat.tip) in DMF (100ml) was stirred at 80°C for 4 hours, filtered warm over dicalite, washed with warm DMF, heated again and filtered warm over dicalite. The solvent was evaporated. The residue was taken up in CH_2Cl_2. The mixture was washed with H_2O. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was co-evaporated with toluene. The residue was crystallized from CH_3CN. The precipitate was filtered off and dried. Yield: 53.5g of intermediate (6) (70%)

Example A5

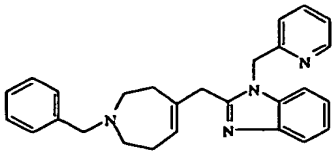
a) Preparation of  (interm. 7)

A mixture of *N*-(1-methylethyl)-2-propanamine (0.098 mol) in THF (100ml) was stirred at -40°C under N_2 flow. BuLi 1.6M in hexane (0.098 mol) was added dropwise. The mixture was stirred at -40°C for 30 min and cooled to -70°C. A mixture of 1-(diethoxymethyl)-2-methyl-1*H*-benzimidazole (0.098 mol) in THF (50ml) was added dropwise and the mixture was stirred for 45 min. A mixture of hexahydro-1-(phenylmethyl)-4*H*-azepin-4-one (0.049 mol) in THF (50ml) was added dropwise at -70°C. The mixture was hydrolized cold and extracted with EtOAc. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2). The pure fractions were collected and the solvent was evaporated (yielding 7.5g). Part of the residue (3.5g) was crystallized from EtOAc. The precipitate was filtered off and dried. Yield: 2.3g of intermediate (7).

b) Preparation of  (interm. 8)

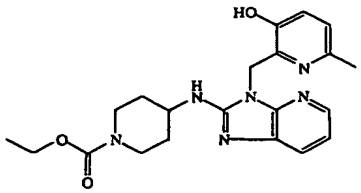
A mixture of intermediate (7) (0.029 mol) in 1,1'-oxybis[2-methoxyethane] (300ml) and H_2SO_4 conc. (20ml) was stirred at 160°C for 24 hours. Ice water was added. The mixture was basified with K_2CO_3 solid and extracted with CH_2Cl_2. The organic layer

was separated, dried, filtered and the solvent was evaporated. Yield: 18g of a mixture of 2 compounds, of which one compound is intermediate (8) (75%).

c) Preparation of  (interm. 9)

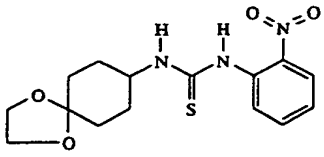
A mixture of intermediate (8), 2-(chloromethyl)pyridine (0.047 mol) and K_2CO_3 (0.0775 mol) in acetonitrile (500ml) was stirred and refluxed for 24 hours. H_2O was added and the mixture was extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. Yield: 15.4g of a mixture of 2 compounds, of which one is intermediate (9).

Example A6

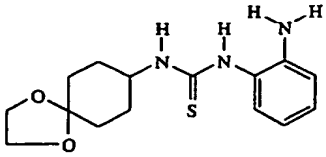
Preparation of  (interm. 10)

N,*N*-diethylethamine (16ml) and then 2-chloromethyl-6-methyl-3-pyridinol (0.0376 mol) were added to a mixture of ethyl 4-[(3*H*-imidazo[4,5-b]pyridin-2-yl)amino]-1-piperdinecarboxylate (0.0376 mol) in DMF (550ml). The mixture was stirred at room temperature for 3 hours and at 50°C overnight. The solvent was evaporated. The residue was poured out into H_2O and CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by HPLC over silica gel (eluent: CH_2Cl_2/C_2H_5OH 95/5 to 70/30). The desired fraction was collected and the solvent was evaporated. Yield: 2.1 g of intermediate (10).

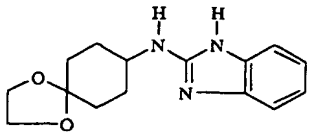
Example A7

a) Preparation of  (interm. 11)

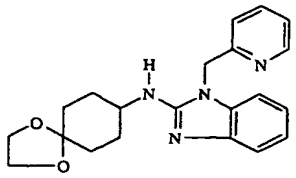
A mixture of 1,4-dioxaspiro[4,5]decan-8-amine (0.28 mol) and 1-isothiocyanato-2-nitrobenzene (0.28 mol) in ethanol (300ml) was stirred at room temperature for 2 hours. The solvent was evaporated. The product was used without further purification. Yield: 90g of intermediate (11).

b) Preparation of  (interm. 12)

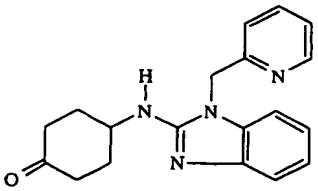
A mixture of intermediate (11) (0.178 mol) in NH_3/CH_3OH (500ml) and THF (100ml) was hydrogenated at room temperature under a 3 bar pressure for 24 hours with Pd/C (52g) as a catalyst. After uptake of H_2 (3 equiv), the catalyst was filtered through celite, washed with CH_3OH and the filtrate was evaporated. The product was used without further purification. Yield: 44g of intermediate (12).

c) Preparation of  (interm. 13)

A mixture of intermediate (12) (0.071 mol), HgO (0.142 mol) and S (0.56g) in ethanol (300ml) was stirred and refluxed for 4 hours, filtered over celite, washed with CH_2Cl_2 and the filtrate was evaporated. The reaction was carried out again using the same quantities. The residues were combined and then purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 94/6/0.5; 20-45 µm). The pure fractions were collected and the solvent was evaporated. Yield: 14.5g of intermediate (13) (43%); mp. >260°C.

d) Preparation of  (interm. 14)

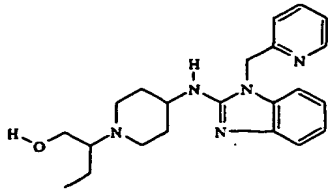
A mixture of intermediate (13) (0.049 mol), 2-(chloromethyl)pyridine (0.0735 mol) and K_2CO_3 (0.196 mol) in acetonitrile (325ml) was stirred and refluxed for 4 hours and then brought to room temperature. The reaction was carried out again using the same quantities. The mixtures were combined. H_2O was added and the mixture was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/ NH_4OH$ 98/2/0.1; 20-45 µm). The pure fractions were collected and the solvent was evaporated [yielding 28.6g (81%)]. Part of this fraction (0.6g) was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 0.46g of intermediate (14); mp. 136°C.

e) Preparation of  (interm. 15)

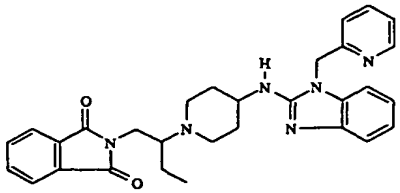
A mixture of intermediate (14) (0.077 mol) in HCl 3N (350ml) was stirred and refluxed for 1 hour, poured out into ice water, basified with K_2CO_3 solid and extracted with CH_2Cl_2. The organic layer was separated, washed with H_2O, dried ($MgSO_4$), filtered

and the solvent was evaporated. Part of the residue (1.5g) was crystallized from CH_3CN and diethyl ether. The precipitate was filtered off and dried. Yield: 0.5g of intermediate (15); mp. 148°C.

Example A8

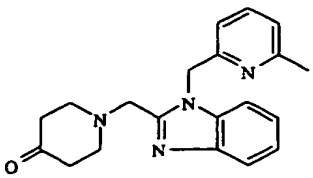
a) Preparation of  (interm. 16)

$LiAlH_4$ (0.023 mol) was added portionwise at 5°C to a solution of (±)-ethyl α-ethyl-4-[[1-(2-pyridylmethyl)-1*H*-benzimidazol-2-yl]amino]-1-piperidineacetate (0.021 mol) in THF (100ml). The mixture was stirred at 5°C for 1 hour. EtOAc was added. The mixture was hydrolized with ice water, filtered over celite, washed with EtOAc, dried ($MgSO_4$), filtered and the solvent was evaporated. Yield: 7.2g of intermediate (16) (88%).

b) Preparation of  (interm. 17)

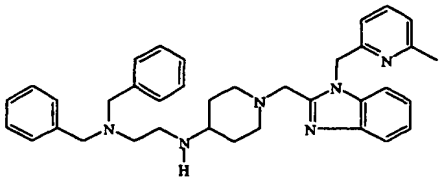
Diethyl azodicarboxylate (0.028 mol) was added slowly at room temperature to a solution of intermediate (16) (0.019 mol), 1*H*-isoindole-1,3(2*H*)-dione (0.028 mol) and triphenyl phosphine (0.028 mol) in THF (200ml). The mixture was stirred at room temperature for 8 hours. The solvent was evaporated till dryness. The residue was dissolved in CH_2Cl_2. The solution was acidified with HCl 3N, basified with NH_4OH and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (12g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/ CH_3OH/NH_4OH 97/3/0.1; 20-45 μm). The pure fractions were collected and the solvent was evaporated. Yield: 5.5g of intermediate (17) (57%).

Example A9

a) Preparation of  (interm. 18)

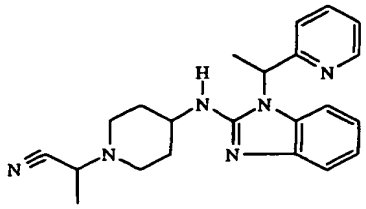
A mixture of 8-[[1-[(6-methyl-2-pyridyl)methyl]-1*H*-benzimidazol-2-yl]methyl]-1,4,8-dioxa-8-azaspiro[4.5]decane (0.0196 mol) in HCl 6N (55ml) and H_2O (55ml) was

stirred and refluxed for 6 hours. Toluene was added. The mixture was poured out on ice, alkalized with a NaOH solution and extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. Yielding a residue of 5.63g. Part of this fraction was suspended in DIPE, filtered off and dried. Yield: 0.32g of intermediate (18) (91%).

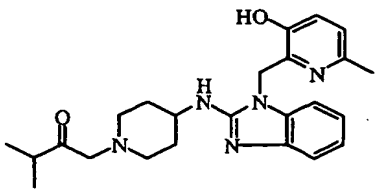
b) Preparation of  (interm. 19)

A mixture of intermediate (18) (0.008 mol) and *N,N*-dibenzylethylenediamine (0.01 mol) in methanol (150ml) was hydrogenated with Pd/C 10% (1g) as a catalyst in the presence of thiophene solution (0.5ml). After uptake of H_2 (1 equiv), the catalyst was filtered off and the filtrate was evaporated. Yield: 5.39g of intermediate (19) (quant.).

Example A10

a) Preparation of  (interm. 20)

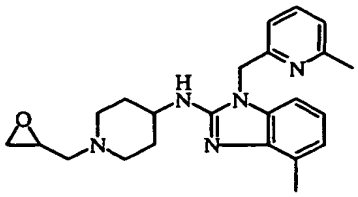
A mixture of (±)-*N*-(4-piperidinyl)-1-[1-(2-pyridyl)ethyl]-1*H*-benzimidazol-2-amine (0.026 mol), 2-chloropropanenitrile (0.039 mol) and K_2CO_3 (0.052 mol) in acetonitrile (100ml) was stirred and refluxed for 8 hours. H_2O was added and the mixture was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (8.5g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 96/4; 20-45 µm). The pure fractions were collected and the solvent was evaporated. Yield: 4.5g of intermediate (20) (46%).

b) Preparation of  (interm. 22)

A mixture of compound 49 (0.0164 mol), 1-bromo-3-methyl-2-butanone (0.03 mol) and K_2CO_3 (0.06 mol) in CH_3CN (100ml) was stirred and refluxed for several hours. H_2O was added. The solvent was evaporated. 4-Methyl-2-pentanone was added. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/(CH_3OH/NH_3)$

98/2). The desired fractions were collected and the solvent was evaporated. Yielding: 2.75g of intermediate 22 (40%).

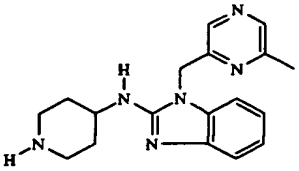
Example A11

Preparation of  (interm. 21)

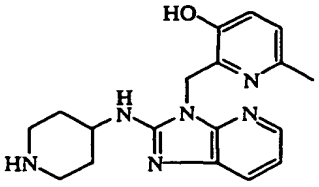
A mixture of compound 90 (0.015 mol), (chloromethyl)oxirane (0.008 mol) and Na_2CO_3 (1.59g) in 4-methyl-2-pentanone (150ml) was heated slowly to 100°C (to 40°C in 1 hour, 70°C in 1 hour), stirred at 100°C overnight, then stirred and refluxed for 20 hours. The solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/(CH_3OH/NH_3) 95/5). Two fractions were collected and their solvents were evaporated. F1 was crystallized from DIPE. The precipitate was filtered off and dried. Yielding: 0.18g of intermediate 21.

Preparation of the final compounds

Example B1

a) Preparation of  (compound 1)

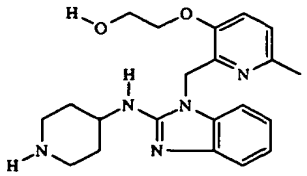
A mixture of intermediate (2) (0.016 mol) in 2-propanol/HCl (10ml) and 2-propanol (100ml) was stirred and refluxed for 2 hours and then cooled. The precipitate was filtered off, washed with DIPE and dried. The residue was taken up in H_2O, NH_3 and CH_3OH and the mixture was extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH_2Cl_2/ (CH_3OH/NH_3) 90/10). The pure fractions were collected and the solvent was evaporated. Yield: 1.8g of compound (1) (35%).

b) Preparation of  (compound 308)

A mixture of intermediate (10) (0.0054 mol) in HBr 48% (50 ml) was stirred and refluxed for 5 hours. The solvent was evaporated. The residue was suspended in DIPE, filtered off and crystallized from ethanol. The solvent was evaporated and the fraction was purified by high-performance liquid chromatography over RP Hyperprep (eluent:

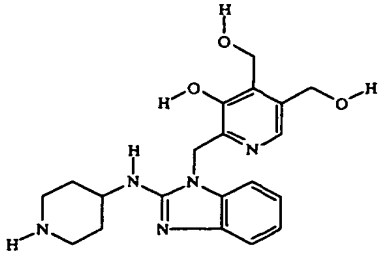
(0.5% NH_4OAc in H_2O)/CH_3CN from 100/0 to 0/100). The pure fractions were collected and the solvent was evaporated. Yield: 0.188 g of compound (308).

Example B2

a) Preparation of  (compound 2)

HCl (1:3); H_2O (1:2)

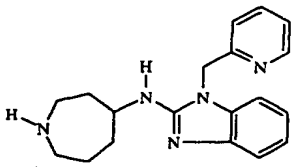
A mixture of intermediate (3) (0.00622 mol) in 2-propanol/HCl (10ml) and 2-propanol (100ml) was stirred and refluxed for 4 hours. The solvent was evaporated. The residue was taken up in H_2O, Na_2CO_3 and CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was dissolved in 2-propanol and DIPE and converted into the hydrochloric acid salt with 2-propanol/HCl. The precipitate was filtered off and dried. This fraction was converted into the free base and purified over silica gel on a glass filter (eluent: CH_2Cl_2/(CH_3OH/NH_3) 90/10). The pure fractions were collected and the solvent was evaporated. The residue was converted into the hydrochloric acid salt (1:3). The precipitate was filtered off and dried. Yield: 0.65g of compound (2) (20%).

b) Preparation of  (compound 3)

HCl (1:3); H_2O (1:2)

A mixture of 1,1-dimethylethyl 4-[[1-[[3,5-dihydro-3,3-dimethyl-9-(phenylmethoxy)-1*H*-[1,3]dioxepino[5,6-c]pyridin-2-yl]methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinecarboxylate (0.00552 mol) in HCl 10N (200ml) was stirred and refluxed for 6 hours. The solvent was evaporated. The residue was suspended in DIPE, filtered off and dried. Yield: 0.58g of compound (3).

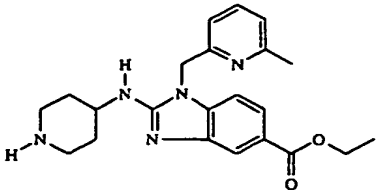
Example B3

Preparation of  (compound 4)

A mixture of intermediate (4) (0.021 mol) and KOH (0.43 mol) in 2-propanol (100ml) was stirred and refluxed overnight. H_2O was added and the mixture was extracted with

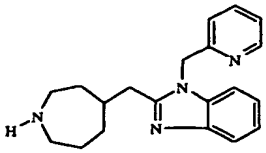
CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. Yield: 6.9g of compound (4) (quant.).

Example B4

Preparation of  (compound 5)

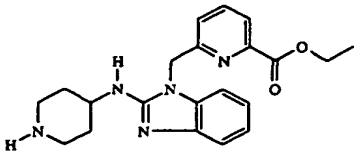
A mixture of intermediate (6) (0.02 mol) in ethanol (120ml) was hydrogenated with Pd/C 10% (2g) as a catalyst. After uptake of H_2 (1 equiv), the catalyst was filtered off and the filtrate was evaporated, yielding a residue of 8g (100%). Part of this fraction (0.7g) was dissolved in ethanol and converted into the hydrochloric acid salt (1:3) with 2-propanol/HCl. DIPE was added. The mixture was stirred. The precipitate was filtered off and dried. Yield: 0.65g of compound (5).

Example B5

Preparation of  (compound 6)

A mixture of intermediate (9) (0.035 mol) in methanol (200ml) was hydrogenated at room temperature under a 3 bar pressure for 48 hours with Pd/C (1.5g) as a catalyst, then hydrogenation was continued at 40°C under a 3 bar pressure for 48 hours. After uptake of H_2 (2 equiv), the catalyst was filtered through celite and the filtrate was evaporated. The residue (12g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/ NH_4OH$ 80/20/3). The pure fractions were collected and the solvent was evaporated. Yield: 3.8g of compound (6) (34%).

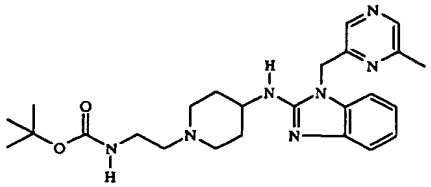
Example B6

Preparation of  (compound 7)

A mixture of 6-[[2-(4-piperidinylamino)-1*H*-benzimidazol-1-yl]methyl]-2-pyridine-carboxylic acid in HCl 36% (5ml) and ethanol (50ml) was stirred and refluxed overnight. The solvent was evaporated. H_2O, $NaHCO_3$ and CH_2Cl_2 were added. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: $CH_2Cl_2/(CH_3OH/NH_3)$ 90/10). The

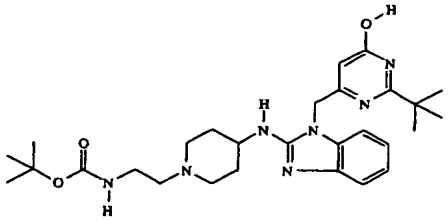
pure fractions were collected and the solvent was evaporated. Yield: 0.83g of compound (7).

Example B7

Preparation of  (compound 8)

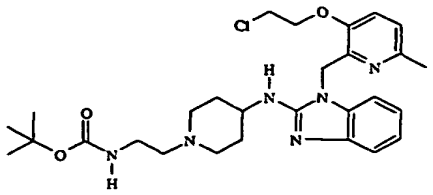
A mixture of compound (1) (0.003 mol), 1,1-dimethylethyl (2-bromoethyl) carbamoate (0.004 mol) and Na_2CO_3 (0.004 mol) in 2-butanone (100 ml) was stirred and refluxed overnight. The reaction mixture was cooled, washed with water and the layers were separated. The organic phase was washed with a NH_4Cl solution. The aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried, filtered and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: $CH_2Cl_2/(CH_3OH/NH_3)$ 97/3). The pure fractions were collected and the solvent was evaporated, yielding a residue of 1.18 g of compound (8) (84%).

Example B8

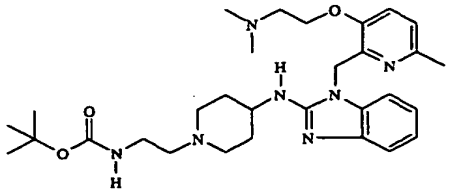
Preparation of  (compound 9)

Reaction under N_2 flow. NaH (0.01 mol) was added to a mixture of 1,1-dimethylethyl [2-[4-(1*H*-benzimidazol-2-ylamino)-1-piperidinyl]ethyl]carbamate (0.01 mol) in DMF p.a. dry (100ml). The mixture was stirred at room temperature for 4 hours. 6-chloro-methyl-2-(1,1-dimethylethyl)-4-pyrimidinol (0.01 mol) in a small amount of DMF p.a. dry was added dropwise. The mixture was stirred at 50°C overnight and then cooled. H_2O (50ml) was added. The solvent was evaporated. The residue was taken up in CH_2Cl_2. The organic solution was washed with H_2O/HOAc, dried ($MgSO_4$), filtered and the solvent was evaporated, to give residue 1. The aqueous layer was taken up in HOAc and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated, to give residue 2. Residue 1 and 2 were combined and purified by column chromatography over RP 18 BDS (eluent: NH_4OAc (0.5% in H_2O)/ CH_3OH/CH_3CN 70/15/15, 0/50/50 and 0/0/100). The pure fractions were collected and the solvent was evaporated, yielding: compound (9).

Example B9

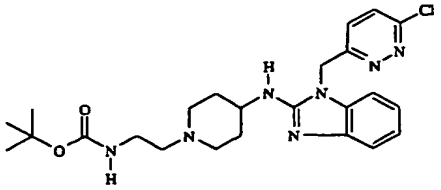
a) Preparation of  (compound 10)

Thionyl chloride (0.03 mol) was added to a mixture of (±)-6-methyl-3-[2-[(tetrahydro-2*H*-pyran-2-yl)oxy]ethoxy]-2-pyridinemethanol (0.015 mol) in CH_2Cl_2 (100ml). Toluene was added and evaporated again. The residue was taken up in DMF (50ml) and then added to a mixture of 1,1-dimethylethyl [2-[4-(1*H*-benzimidazol-2-ylamino)-1-piperidinyl]ethyl]carbamate (0.015 mol) and NaH (0.06 mol) in DMF (200ml). The mixture was stirred at 50°C overnight. The solvent was evaporated. The residue was taken up in H_2O and CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH_2Cl_2/ (CH_3OH/NH_3) 99/1). The pure fractions were collected and the solvent was evaporated. The residue was suspended in petroleum ether. The precipitate was filtered off and dried. Yield: 1.55g of compound (10) (20%).

b) Preparation of  (compound 11)

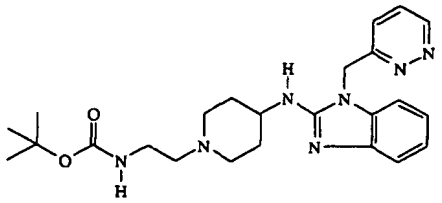
A mixture of compound (10) (0.00147 mol) and $NH(CH_3)_2$ gas (20g) in THF (100ml) was stirred at 125°C for 16 hours. The solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH_2Cl_2/(CH_3OH/NH_3) 95/5). The pure fractions were collected and the solvent was evaporated. Yield: 0.43g of compound (11) (53%).

Example B10

a) Preparation of  (compound 12)

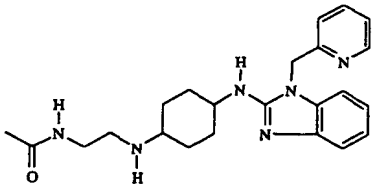
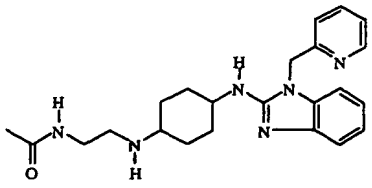
1-Bromo-2,5-pyrrolidinedione (0.088 mol) and then dibenzoyl peroxide (cat.quant.) were added to a solution of 3-chloro-6-methylpyridazine (0.08 mol) in CCl_4 (mol. sieves) (200ml). The mixture was stirred and refluxed for 6 hours and then filtered over dicalite. 1-Bromo-2,5-pyrrolidinedione (0.088 mol) and dibenzoyl peroxide (cat.quant.) were added again. The mixture was stirred and refluxed overnight and

filtered over dicalite. The solvent was evaporated at a temperature below 40°C. The residue was dissolved in DMF (70ml) and added to a mixture of 1,1-dimethylethyl [2-[4-(1*H*-benzimidazol-2-ylamino)-1-piperidinyl]ethyl]carbamate (0.0214 mol) and NaH (0.0235 mol) in DMF (190ml), previously stirred at room temperature for 1 hour and at 40°C for 1 hour. The resulting mixture was stirred at 50°C overnight. The solvent was evaporated. H_2O and CH_2Cl_2 were added. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/(CH_3OH/NH_3) 97/3). The pure fractions were collected and their solvents were evaporated. Yield: 1.21g of compound (12).

b) Preparation of  (compound 13)

A mixture of compound (12) (0.0025 mol), CaO (2g) and Pd/C (1g) in 1-butanethiol (2ml) and THF (100ml) was stirred at room temperature for the weekend. The solvent was evaporated. Yield: 1g of compound (13) (88%).

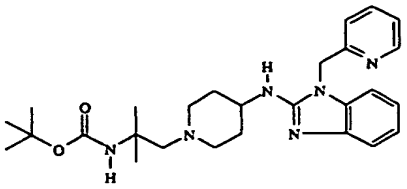
Example B11

Preparation of  and 

(cis) (compound 14) (trans) compound (15)

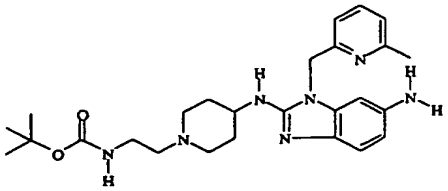
A mixture of intermediate (15) (0.031 mol) and *N*-(2-aminoethyl)acetamide (0.093 mol) in methanol (300ml) was hydrogenated at 30°C under a 3 bar pressure for 12 hours with Pd/C (5g) as a catalyst. After uptake of H_2 (1 equiv), the catalyst was filtered through celite, washed with CH_3OH and the filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/ CH_3OH/NH_4OH 92/8/0.5; 20-45 µm). Two pure fractions were collected and their solvents were evaporated, yielding a residue of 2.8g (22%) and 9g (71%). Parts of these fractions (0.6g, 0.8g) were crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 0.52g of compound (14); mp. 126°C and 0.53g of compound (15); mp. 200°C.

Example B12

Preparation of  (compound 16)

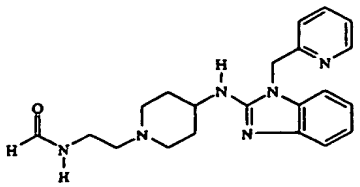
$NaBH_3CN$ (0.048 mol) was added portionwise at 5°C to a solution of *N*-4-piperidinyl-1-(2-pyridylmethyl)-1*H*-benzimidazol-2-amine dihydrochloride (0.032 mol) and 1,1-dimethylethyl (1,1-dimethyl-2-oxoethyl)carbamoate (0.032 mol) in methanol (100ml). The mixture was stirred at room temperature for 8 hours and hydrolized at 5°C with ice water. Methanol was evaporated. The residue was extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (13g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/ NH_4OH$ 95/5/0.1; 20-45 µm). The pure fractions were collected and the solvent was evaporated. Yield 2.2g of compound (16) (14%).

Example B13

Preparation of  (compound 17)

A mixture of 1,1-dimethylethyl [2-[4-[[1-[(6-methyl-2-pyridyl)methyl]-6-nitro-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]carbamate (0.0084 mol) in methanol (150ml) was hydrogenated at 50°C with Pt/C 5% (1g) as a catalyst in the presence of thiophene solution (1ml). After uptake of H_2 (3 equiv), the catalyst was filtered off and the filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/(CH_3OH/NH_3)$ 99/1 to 97.5/2.5). The pure fractions were collected and the solvent was evaporated. Yield: 3.3g of compound (17) (82%).

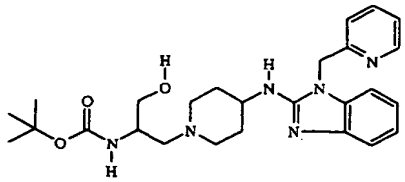
Example B14

Preparation of  (compound 18)

A mixture of *N*-[1-(2-aminoethyl)-4-piperidinyl]-1-[(2-pyridyl)methyl]-1*H*-benzimidazol-2-amine (0.143 mol) in HCOOH (50ml) was stirred and refluxed for 3 hours. The solvent was evaporated till dryness. The residue was dissolved in CH_2Cl_2. The mixture was basified with Na_2CO_3, filtered and the filtrate was evaporated till

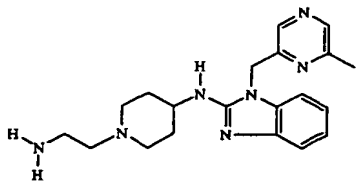
dryness. The residue (4.9g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 92/8/1; 20-45 µm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from 2-propanone. The precipitate was filtered off and dried. Yield: 2.8g of compound (18) (51%); mp. 146°C.

Example B15

Preparation of  (compound 19)

$LiAlH_4$ (0.0065 mol) was added portionwise at 5°C to a solution of (±)-1,1-dimethylethyl [1-(methoxycarbonyl)-2-[4-[[1-(2-pyridylmethyl)-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]carbamate (0.0059 mol) in THF (30ml). The mixture was stirred at 5°C for 1 hour. EtOAc was added. The mixture was hydrolized with ice water, filtered over celite and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (2.8g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/ NH_4OH$ 92/8/0.5; 15-40 µm). The pure fractions were collected and the solvent was evaporated. Yield: 1.55g of compound (19) (56%).

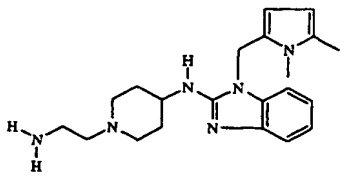
Example B16

Preparation of  (compound 20)

HCl (1:3); H_2O (1:2)

A mixture of compound (8) (0.00215 mol) in 2-propanol/HCl (10ml) and 2-propanol (100ml) was stirred and refluxed overnight. The solvent was evaporated partially. The precipitate was filtered off, washed with DIPE and dried. This fraction was crystallized from ethanol. The precipitate was filtered off and dried. Yield: 0.58g of compound (20) (51%).

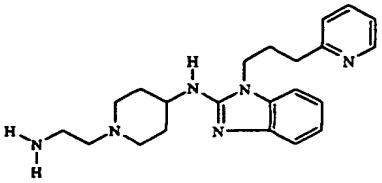
Example B17

Preparation of  (compound 21)

H_2O (1:1)

A mixture of 1,1-dimethylethyl [2-[4-[[1-(1,5-dimethyl-1*H*-pyrrol-2-yl)-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]carbamate (0.002 mol) and KOH (1g) in sec. butanol (25ml) was stirred and refluxed for 1 hour. The solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/(CH_3OH/NH_3) 90/10). The pure fractions were collected and the solvent was evaporated. The residue was suspended in DIPE. The precipitate was filtered off and dried. Yield: 0.57g of compound (21).

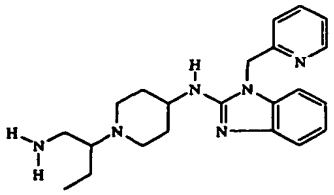
Example B18

Preparation of  (compound 22)

HCl (1:4); H_2O (1:2)

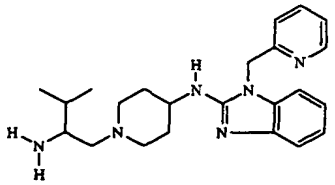
A mixture of 2-[2-[4-[[1-[3-(2-pyridyl)propyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-1*H*-isoindole-1,3(2*H*)-dione (0.005 mol) in HCl 6N (120ml) and HOAc (60ml) was stirred and refluxed for 30 hours and then cooled on an ice bath. A NaOH solution was added carefully dropwise until pH > 7. The mixture was extracted with CH_2Cl_2 and then separated into its layers. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with H_2O, separated again, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was taken up in a small amount of 2-propanol and converted into the hydrochloric acid salt (1:4) with 2-propanol/HCl 6N. DIPE was added. The precipitate was filtered off, washed with DIPE and dried. Yield: 1.95g of compound (22) (70%).

Example B19

Preparation of  (compound 23)

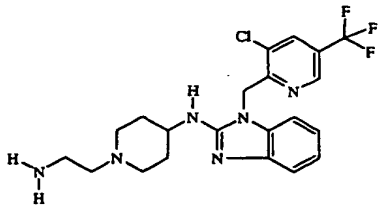
A mixture of intermediate (17) (0.01 mol) in hydrazine (5ml) and ethanol (50ml) was stirred and refluxed for 30 min. The solvent was evaporated. The residue was dissolved in CH_2Cl_2. The organic solution was washed with H_2O, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (4.8g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 89/10/1; 15-40 µm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 51.7g of compound (23) (45%); mp. 112°C.

Example B20

Preparation of  (compound 24)

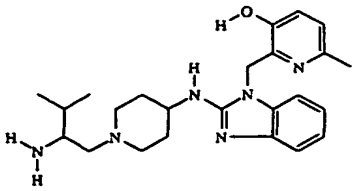
A mixture of 3-methyl-1-[4-[[1-(2-pyridylmethyl)-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]-2-butanone (0.01 mol) and benzenemethanamine (0.031 mol) in methanol (50ml) was hydrogenated at 40°C under a 3 bar pressure for 24 hours with Pd/C (0.4g) as a catalyst. After uptake of H_2 (1 equiv), the catalyst was filtered through celite, washed with CH_3OH and CH_2Cl_2 and the filtrate was evaporated. The residue (5g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 93/7/1; 15-40 µm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from pentane. The precipitate was filtered off and dried. Yield: 1g of compound (24) (21%); mp. 115°C.

Example B21

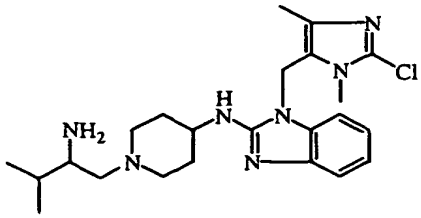
Preparation of  (compound 25)

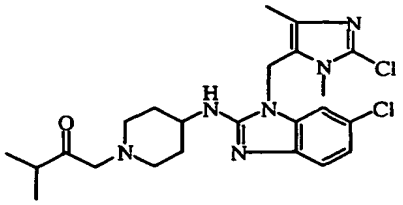
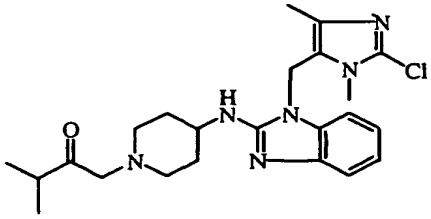
Reaction under N_2 atmosphere. Na_2CO_3 (0.250 g) was added to 1,1-dimethylethyl [2-[4-(1*H*-benzimidazol-2-ylamino)-1-piperidinyl]ethyl]carbamate (0.0028 mol) in DMF (10 ml). The mixture was stirred for 4 hours at room temperature. The reaction mixture was divided over 5 tubes. 2-Chloromethyl-3-chloro-5-trifluoropyridine (0.100 g) was added to each tube and the resulting reaction mixture was stirred overnight at 50 °C. The mixture was acidified with HCl/2-propanol, then stirred for 3 hours at 90°C. The mixture was alkalized with NH_3/CH_3OH and the desired compound was isolated and purified by high-performance liquid chromatography over a Prochrom D.A.C.-column with Hypersil 'BDS' HS C18 (100 g, 8 µm, 100 Å; eluent gradient: ((0.5% NH_4OAc in H_2O)/CH_3OH/CH_3CN (0 min) 70/15/15, (10.31 min) 0/50/50, (16.32 min) 0/0/100, (16.33 min-end) 70/15/15). The desired fractions were collected and the solvent was evaporated. Yield: 0.020 g of compound (25).

Example B22

a) Preparation of  (compound 26)

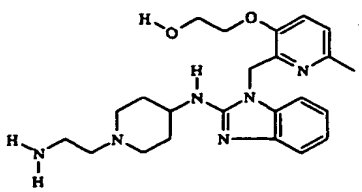
A mixture of 1-[4-[[1-[(3-hydroxy-6-methyl-2-pyridyl)methyl]-1*H*-benzimidazol-2-yl]-amino]-1-piperidinyl]-3-methyl-2-butanone (0.0065 mol) in CH_3OH/NH_3 (300ml) was hydrogenated at room temperature with Rh/Al_2O_3 (1g) as a catalyst in the presence of CH_3OH/NH_3 (3ml). After uptake of H_2 (1 equiv), the catalyst was filtered off and the filtrate was evaporated. The residue was purified over silica gel on a glass filter (eluent: $CH_2Cl_2/(CH_3OH/NH_3)$ 95/5 to 90/10). The pure fractions were collected and the solvent was evaporated. Yield: 1.52g of compound (26) (55%).

b) Preparation of  (compound 298)

A mixture of  and 

(prepared analogous to the procedure described in example A10b; 0.6 g) in NH_3/CH_3OH (100 ml) was hydrogenated for 16 hours at 50°C with Rh/C (0.5 g) as a catalyst in the presence of thiophene solution (1 ml). After uptake of H_2 (1 equiv), the catalyst was filtered off and the filtrate was evaporated. The residue was purified by high-performance liquid chromatography over Kromasil C18 (100 Å; eluent: NH_4OAc 0.5% H_2O/CH_3CN 75%, 25% CH_3OH to CH_3CN 100%). Two pure fraction groups were collected and their solvent was evaporated. Yield : 0.165 g of compound 298.

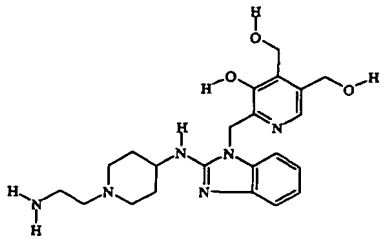
Example B23

Preparation of  (compound 27)

HCl (1:3); H_2O (1:1)

A mixture of (±)-1,1,dimethylethyl [2-[4-[[1-[[6-methyl-3-[2-[(tetrahydro-2*H*-pyran-2-yl)oxy]ethoxy]-2-pyridyl]methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-carbamate (0.0014 mol) in 2-propanol/HCl (5ml) and 2-propanol (50ml) was stirred and refluxed for 4 hours and taken up in H_2O, Na_2CO_3 and CH_2Cl_2. The organic layer was separated. 2-Propanol/HCl (5ml) and 2-propanol (50ml) were added again. The mixture was stirred and refluxed for 1 hour and converted into the hydrochloric acid salt. The precipitate was filtered off and dried. The residue was purified over silica gel on a glass filter (eluent: CH_2Cl_2/ (CH_3OH/NH_3) 90/10). The pure fractions were collected and the solvent was evaporated. The residue was converted into the hydrochloric acid salt. The precipitate was filtered off and dried. Yield: 0.18g of compound (27) (23%).

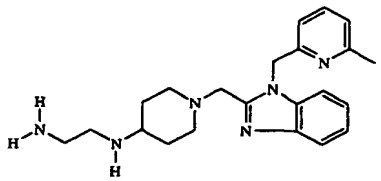
Example B24

Preparation of  (compound 28)

HCl (1:1)

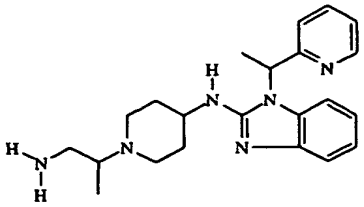
A mixture of 1,1-dimethylethyl [2-[4-[[1-[[3,5-dihydro-3,3-dimethyl-9-(phenyl-methoxy)-1*H*-[1,3]dioxepino[5,6-c]pyridin-2-yl]methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]carbamate (0.00213 mol) in HCl 10N (100ml) was stirred and refluxed for 4 hours. The solvent was evaporated. The residue was suspended in DIPE. The precipitate was filtered off and dried. Yield: 0.9g of compound (28).

Example B25

Preparation of  (compound 29)

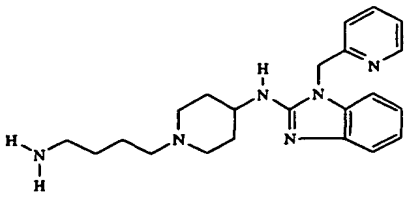
A mixture of intermediate (19) (0.008 mol) in methanol (150ml) was hydrogenated with Pd/C (1g) as a catalyst. After uptake of H_2 (1 equiv), the catalyst was filtered off and the filtrate was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH_2Cl_2/ (CH_3OH/NH_3) 95/5, 93/7 to 90/10). The pure fractions were collected and the solvent was evaporated. Yield: 1.81g of compound (29) (60%).

Example B26

Preparation of  (compound 30)

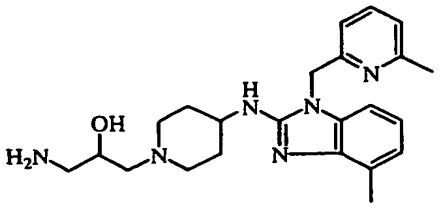
$LiAlH_4$ (0.014 mol) was added portionwise at 5°C to a solution of intermediate (20) (0.012 mol) in THF (50ml). The mixture was allowed to warm to room temperature and then stirred at room temperature for 48 hours. EtOAc was added. The mixture was hydrolized with ice water, filtered over celite, washed with EtOAc and the filtrate was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (3g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/ NH_4OH$ 87/13/1; 15-40 µm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from DIPE. The precipitate was filtered off and dried. Yield: 0.75g of compound (30) (16%); mp. 85°C.

Example B27

Preparation of  (compound 31)

A mixture of 4-[[1-(2-pyridylmethyl)-1*H*-benzimidazol-2-yl]amino]-1-piperidine-butanenitrile (0.01 mol) in CH_3OH/NH_3 (80ml) was hydrogenated at room temperature under a 3 bar pressure overnight with Raney Nickel (3.8g) as a catalyst. After uptake of H_2 (2 equiv), the catalyst was filtered through celite and the filtrate was evaporated. The residue was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 2.9g of compound (31) (76%); mp. 94°C.

Example B28

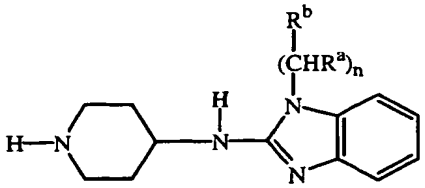
Preparation of  (compound 303)

A mixture of intermediate 21 (0.001 mol) in CH_3OH/NH_3 (100ml) was stirred at room temperature for 20 hours and at 100°C for 16 hours. The solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/

(CH_3OH/NH_3) 90/10). The pure fractions were collected and the solvent was evaporated. The residue was dried. Yielding: 0.11g of compound 303.

Tables 1 to 16 list the compounds of formula (I) which were prepared according to one of the above examples.

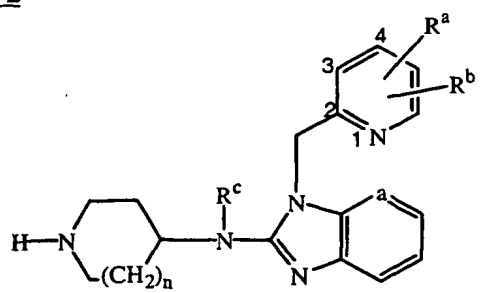
Table 1



Co. No.	Ex. No.	n	R^a	R^b	Physical data
32	B1a	1	H	1,4-dimethyl-1*H*-imidazol-5-yl	H_2O (1:2)
33	B1a	1	H	1,4-dimethyl-5-[-$COOC_2H_5$]-1*H*-imidazol-2-yl	HCl (1:3)
34	B1a	1	H	2-bromo-5-pyridyl	
35	B1a	1	CH_3	2-pyrazinyl	
36	B1a	1	ethyl	2-pyrazinyl	
37	B1a	1	H	2-pyridyl	HCl (1:2); mp. >160°C
38	B1a	1	CH_3	2-pyridyl	
39	B1a	2	H	2-pyridyl	HCl (1:3); H_2O (1:2)
40	B1b	2	H	2-pyridyl	
41	B1b	3	H	2-pyridyl	HBr (1:3)
42	B1a	0	-	2-pyrimidinyl	
43	B1a	1	H	2-pyrimidinyl	HCl (1:3); H_2O (1:1)
44	B1a	1	H	3,5,6-trimethyl-2-pyrazinyl	
45	B1a	1	H	3-[C_2H_5-O-$(CH_2)_2$-O]-6-methyl-2-pyridyl	HCl (1:3); H_2O (1:3)
46	B1a	1	H	3-amino-2-pyridyl	HCl (1:3); H_2O (1:2)
47	B1a	1	H	3-amino-2-pyridyl	
48	B1a	1	H	3-hydroxy-2-pyridyl	HCl (1:3); H_2O (1:1)
49	B1a	1	H	3-hydroxy-6-methyl-2-pyridyl	HCl (1:3); H_2O (1:3)
50	B1a	1	H	3-hydroxy-6-pyridazinyl	HCl (1:2); H_2O (1:1)
51	B1a	1	H	3-methoxy-6-methyl-2-pyridyl	HCl (1:3); H_2O (1:2)
52	B1a	1	H	3-methoxy-6-methyl-2-pyridyl	
53	B1a	1	H	3-methyl-2-pyrazinyl	

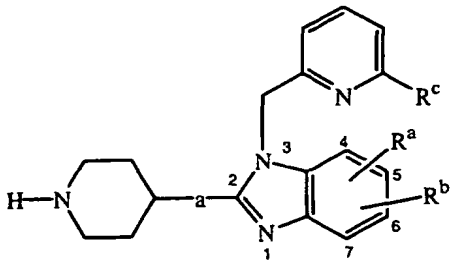
Co. No.	Ex. No.	n	R^a	R^b	Physical data
3	B2b	1	H	3-OH-4,5-(-CH_2-OH)$_2$-2-pyridyl	HCl (1:3); H_2O (1:2)
54	B1a	1	H	3-pyridazinyl	
55	B3	1	H	1,5-(CH_3)$_2$-1*H*-pyrrol-2-yl	
56	B1a	1	H	4,6-dimethyl-2-pyridyl	
57	B1a	1	H	4-chloro-2-pyridyl	
58	B1a	1	H	4-methoxy-2-pyridyl	
59	B1a	1	H	4-methyl-1*H*-imidazol-5-yl	HCl (1:3); H_2O (1:1)
60	B1a	1	H	4-pyridyl	HCl (1:3); H_2O (1:1)
61	B1a	1	H	4-pyridyl	
62	B1a	1	H	4-pyrimidinyl	
63	B1a	1	H	5-chloro-1-methyl-1*H*-imidazol-2-yl	
64	B1a	1	H	5-methyl-2-pyrazinyl	HCl (1:1)
65	B1a	1	H	5-methyl-2-pyrazinyl	
66	B1a	1	H	6-(-CH_2-O-CH_3)- 2-pyridyl	HCl (1:2); H_2O (1:3)
67	B1a	1	H	6-(hydroxymethyl)-2-pyridyl	
68	B1a	1	H	6-[-CO-N(CH_3)$_2$]-2-pyridyl	
69	B1a	1	H	6-bromo-2-pyridyl	HCl (1:2)
70	B1a	1	H	6-bromo-2-pyridyl	
71	B1a	1	H	6-chloro-2- pyridyl	HCl (1:2)
72	B1a	1	H	6-HOOC-2-pyridyl	
73	B1a	1	CH_3	6-hydroxymethyl-2-pyridyl	HCl (1:3); H_2O (1:1)
74	B1a	1	H	6-methoxy-2-pyridyl	
1	B1a	1	H	6-methyl-2-pyrazinyl	
75	B1a	1	CH_3	6-methyl-2-pyrazinyl	
2	B2a	1	H	6-methyl-3-[-O-(CH_2)$_2$-OH]-2-pyridyl	HCl (1:3); H_2O (1:2)
76	B1a	1	H	6-methyl-3-[-O-(CH_2)$_2$-N(CH_3)$_2$]-2-pyridyl	HCl (1:4); H_2O (1:1)
7	B6	1	H	6-(-$COOC_2H_5$)-2-pyridyl	

Table 2



Co. No.	Ex. No.	n	a	R^a	R^b	R^c	Physical data
78	B1a	1	CH	H	H	CH_3	-
4	B3	2	CH	H	H	H	-
81	B16	1	CH	H	H	$-CH_2$-phenyl	-
308	B1b	1	N	3-OH	6-CH_3	H	-

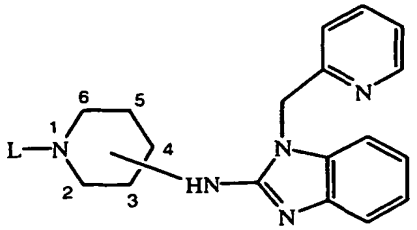
Table 3

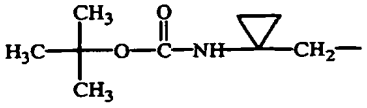
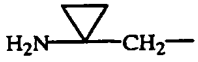


Co. No.	Ex. No.	a	R^a	R^b	R^c	Physical data
82	B4	CH_2	5-OCH_3	6-OCH_3	H	
83	B1b	NH	5-Cl	6-Cl	CH_3	HBr (1:3)
84	B1b	NH	5-CH_3	6-CH_3	CH_3	HBr (1:3)
85	B1b	NH	4-Cl	H	CH_3	HBr (1:3)
86	B1b	NH	7-Cl	H	CH_3	HBr (1:3); H_2O (1:1)
87	B1b	NH	6-NO_2	H	CH_3	HBr (1:3); H_2O (1:1)
88	B1b	NH	7-CH_3	H	CH_3	HBr (1:3)
89	B1b	NH	5-NO_2	H	CH_3	HBr (1:3); H_2O (1:1)
90	B1b	NH	7-CH_3	H	CH_3	
91	B1b	NH	4-CH_3	H	CH_3	HBr (1:3)
92	B1b	NH	4-CH_3	H	CH_3	
93	B1b	NH	5-CF_3	H	CH_3	
94	B1b	NH	6-CF_3	H	CH_3	
95	B1b	NH	6-Cl	H	CH_3	

Co. No.	Ex. No.	a	R^a	R^b	R^c	Physical data
96	B1b	NH	5-Cl	H	CH_3	
5	B4	NH	6-(-$COOC_2H_5$)	H	CH_3	
97	B4	NH	6-(-$COOC_2H_5$)	H	CH_3	HCl (1:3); H_2O (1:1)
98	B4	NH	6-(-CH_2-OH)	H	CH_3	HCl (1:3); H_2O (1:2)
99	B4	NH	6-(-CH_2-OH)	H	CH_3	
100	B1a	CH[$N(CH_3)_2$]	H	H	CH_3	HCl (1:4); H_2O (1:1)

Table 4



Co. No.	Ex. No.	*	L	Physical data
101	B4	4	3-piperidinyl	HCl (1:4); H_2O (1:2)
102	B4	3	H	
18	B14	4	-$(CH_2)_2$-NH-CHO	mp. 146°C
103	B7	4		
104	B16	4		HCl (1:4); H_2O (1:2); mp. 226°C
105	B16	4	-CH_2-$C(CH_3)_2$-NH_2	HCl (1:3); H_2O (1:2); mp. 195°C
106	B16	4	-CH_2-$CH(CH_2OH)$- NH_2	HCl (1:4); H_2O (1:2); mp. 200°C
23	B19	4	-$CH(C_2H_5)$-CH_2-NH_2	mp. 112°C
107	B19	4	-$CH(C_6H_5)$-$CH(C_6H_5)$-NH_2	(A); mp. 106°C
108	B19	4	-$CH(C_6H_5)$-$CH(C_6H_5)$-NH_2	(B); mp. 98°C
109	B19	4	2-aminocyclohexyl	mp. 116°C
110	B19	4	-CH(phenylmethyl)-CH_2-NH_2	mp. 168°C
111	B19	4	-$CH[C(CH_3)_3]$-CH_2-NH_2	mp. 133°C
112	B19	4	-$CH[CH_2$-$N(CH_3)_2]$-CH_2-NH_2	mp. 112°C
113	B19	4	-CH_2-$CH(NH_2)$-phenyl	mp. 128°C
114	B19	4	-$CH[CH_2$-(1-piperidinyl)]-CH_2-NH_2	HCl (1:4); mp. 203°C
115	B19	4	-CH_2-CH(cyclopropyl)-NH_2	H_2O (1:2); mp. 84°C
24	B20	4	-CH_2-$CH[CH(CH_3)_2]$-NH_2	mp. 115°C

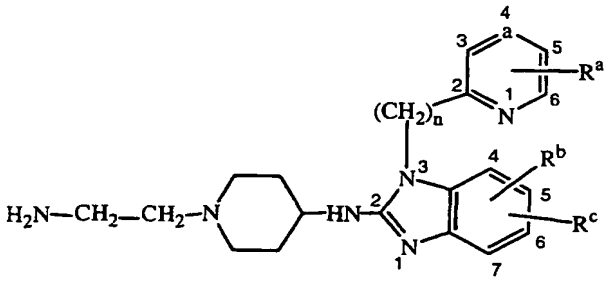
Co. No.	Ex. No.	*	L	Physical data
116	B20	4	$-CH_2-CH(CH_3)-NH_2$	H_2O (1:1)
117	B20	4	$-CH(CH_3)-CH(CH_3)-NH_2$	(B); mp. 114°C
118	B20	4	$-CH_2-CH(C_2H_5)-NH_2$	mp. 140°C
119	B20	4	$-CH_2-CH(cycloC_6H_{11})-NH_2$	mp. 134°C
120	B20	4	$-CH(CH_3)-CH(CH_3)-NH_2$	(A); HCl (1:4); H_2O (1:4); mp. 214°C
121	B20	4	$-CH_2-CH(NH_2)-CH_2-CH(CH_3)_2$	mp. 124°C
122	B20	4	$-CH_2-CH(NH_2)-(CH_2)_3-CH_3$	mp. 142°C
123	B20	4	$-CH_2-CH(NH_2)-(CH_2)_2-CH(CH_3)_2$	mp. 152°C
124	B20	4	$-CH_2-CH(NH_2)-(CH_2)_2-CH_3$	mp. 146°C
125	B20	4	$-CH_2-CH(NH_2)-(CH_2)_7-CH_3$	mp. 136°C
126	B20	4	$-CH_2-CH(NH_2)-(CH_2)_2$-phenyl	mp. 136°C
127	B20	4	$-CH_2-CH(NH_2)-CH_2-C(CH_3)_3$	HCl (1:4); H_2O (1:1); mp. 244°C
128	B20	4	$-CH_2-CH(NH_2)-CH(CH_3)(C_2H_5)$	(A); H_2O (1:1); mp. 80°C
129	B20	4	$-CH_2-CH(NH_2)-CH(CH_3)(C_2H_5)$	(B); mp. 90°C
130	B20	4	$-CH_2-CH(NH_2)-(CH_2)_2$-(4-methoxyphenyl)	mp. 100°C
131	B1a	4	$-CH_2-CH(NH_2)$-(4-piperidinyl)	HCl (1:5); H_2O (1:1); mp. 269°C
31	B27	4	$-(CH_2)_4-NH_2$	mp. 94°C
132	B27	4	$-CH(CH_3)-CH_2-NH_2$	mp. 142°C
133	B27	3	$-(CH_2)_2-NH_2$	H_2O (1:1); mp. 90°C
134	B16	4	$-(CH_2)_3-NH_2$	HCl (1:4); H_2O (1:1); mp. >250°C

* = position piperidinyl

(A) indicates the first isolated stereoisomeric form

(B) indicates the second isolated stereoisomeric form

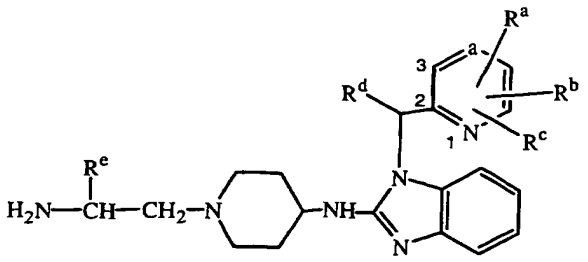
Table 5



Co. No.	Ex. No.	n	a	R^a	R^b	R^c	Physical data
135	B1a	1	CH	6-[-$COOCH(CH_3)_2$]	H	H	

Co. No.	Ex. No.	n	a	R^a	R^b	R^c	Physical data
136	B1a	1	CH	6-[-$COOC_2H_5$]	H	H	
137	B16	1	CH	6-CH_2OH	H	H	
138	B16	1	CH	6-CH_3	5-Cl	6-Cl	HCl (1:4); H_2O (1:1)
139	B16	1	N	3-CH_3	H	H	HCl (1:3); H_2O (1:1)
20	B16	1	N	6-CH_3	H	H	HCl (1:3); H_2O (1:2)
140	B16	1	N	5-CH_3	H	H	HCl (1:4); H_2O (1:2)
141	B16	2	CH	H	H	H	HCl (1:4); H_2O (1:1)
142	B16	1	CH	6-CH_3	5-CH_3	6-CH_3	HCl (1:4); H_2O (1:2); 2-propanolate (1:1)
143	B16	1	CH	6-CH_3	4-Cl	H	HCl (1:4); H_2O (1:2)
144	B16	1	CH	6-CH_3	7-Cl	H	HCl (1:4); H_2O (1:2)
145	B16	1	CH	6-CH_3	6-NO_2	H	HCl (1:4); H_2O (1:3)
146	B16	1	CH	6-CH_3	6-NH_2	H	HCl (1:5); H_2O (1:2)
147	B16	1	CH	6-CH_3	5-NO_2	H	HCl (1:4); H_2O (1:1)
148	B16	1	CH	6-CH_3	5-NH_2	H	HCl (1:5); H_2O (1:1)
149	B16	1	CH	6-CH_3	7-CH_3	H	
151	B16	1	CH	6-Cl	H	H	
153	B16	1	CH	6-Br	H	H	
154	B16	1	CH	6-OH	H	H	
155	B16	1	CH	6-OCH_3	H	H	
156	B16	1	CH	4-Cl	H	H	HCl (1:4); H_2O (1:1)
157	B16	1	CH	4-OCH_3	H	H	HCl (1:4); H_2O (1:2); 2-propanolate (1:1)
158	B16	1	CH	6-CH_2OCH_3	H	H	HCl (1:4); H_2O (1:2)
159	B16	1	N	5-$COOC_2H_5$	H	H	HCl (1:3); H_2O (1:1)
160	B16	1	CH	6-CH_3	4-CH_3	H	HCl (1:4); H_2O (1:2)
161	B16	1	CH	6-CH_3	6-$COOC_2H_5$	H	HCl (1:4); H_2O (1:1)
162	B16	1	CH	6-CH_3	6-CH_2OH	H	H_2O (1:1)
163	B16	1	CH	6-CH_3	5-CF_3	H	HCl (1:4); H_2O (1:2)
164	B16	1	CH	6-CH_3	6-CF_3	H	HCl (1:4); H_2O (1:1)
165	B16	1	CH	6-$CON(CH_3)_2$	H	H	HCl (1:3); H_2O (1:2)
166	B16	1	CH	6-CH_3	5-Cl	H	HCl (1:4); H_2O (1:2)
22	B18	3	CH	H	H	H	HCl (1:4); H_2O (1:2)
167	B27	1	CH	6-CH_3	H	H	
305	B16	1	CH	6-CH_3	5-CH_3	H	-
306	B16	1	CH	6-CH_3	6-Cl	H	HCl (1:4)

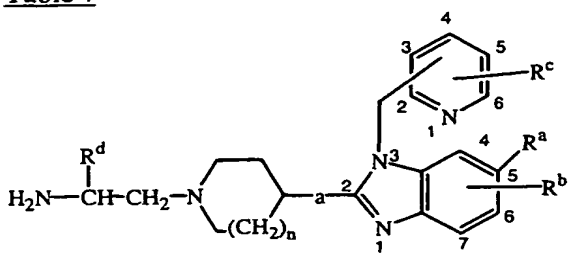
Table 6



Co. No.	Ex. No.	a	R^a	R^b	R^c	R^d	R^e	Physical data
168	B27	CH	3-OH	H	H	H	H	-
169	B1a	CH	3-[-O-$(CH_2)_2$-$N(CH_3)_2$]	6-CH_3	H	H	H	HCl (1:5); H_2O (1:2)
152	B16	CH	H	H	H	CH_3	H	HCl (1:4); H_2O (1:3)
170	B20	CH	3-NH_2	H	H	H	$CH(CH_3)_2$	HCl (1:4); H_2O (1:3)
171	B20	N	5-CH_3	H	H	H	CH_3	mp. 175°C
172	B20	N	6-CH_3	H	H	H	CH_3	mp. 126°C
173	B20	N	3-CH_3	5-CH_3	6-CH_3	H	CH_3	HCl (1:4); H_2O (1:3); mp. 208°C
174	B20	N	3-CH_3	5-CH_3	6-CH_3	H	$CH(CH_3)_2$	mp. 124°C
175	B16	N	H	H	H	CH_3	H	HCl (1:3)
176	B16	N	3-CH_3	5-CH_3	6-CH_3	H	H	HCl (1:4); H_2O (1:1); 2-propanolate (1:1)
177	B16	N	H	H	H	ethyl	H	HCl (1:3); H_2O (1:1)
178	B16	N	6-CH_3	H	H	CH_3	H	HCl (1:3); H_2O (1:1)
179	B16	CH	4-CH_3	6-CH_3	H	H	H	HCl (1:4); H_2O (1:2)
180	B16	CH	6-Cl	H	H	CH_3	H	HCl (1:3); H_2O (1:1)
181	B16	CH	3-OH	6-CH_3	H	H	H	HCl (1:3); H_2O (1:2)
182	B16	CH	3-OCH_3	6-CH_3	H	H	H	
183	B16	CH	6-CH_2OH	H	H	CH_3	H	HCl (1:4); H_2O (1:1)
184	B16	CH	3-[O-$(CH_2)_2$-OC_2H_5	6-CH_3	H	H	H	HCl (1:4); H_2O (1:2)
185	B16	CH	3-OCH_2CH_2Cl	6-CH_3	H	H	H	HCl (1:3); H_2O (1:2)
186	B20	CH	H	H	H	CH_3	CH_3	HCl (1:3); H_2O (1:3); mp. 170°C
187	B20	N	6-CH_3	H	H	H	$CH(CH_3)_2$	HCl (1:3); H_2O(1:3); mp. 200°C
188	B20	CH	H	H	H	CH_3	$CH(CH_3)_2$	mp. 233°C
189	B20	N	5-CH_3	H	H	H	$CH(CH_3)_2$	mp. 114°C
190	B20	CH	H	H	H	H	$CH(CH_3)_2$	mp. 50°C

Co. No.	Ex. No.	a	R^a	R^b	R^c	R^d	R^e	Physical data
25	B21	CH	3-Cl	5-CF_3	H	H	H	
26	B22a	CH	3-OH	6-CH_3	H	H	$CH(CH_3)_2$	
27	B23	CH	3-O-$(CH_2)_2$-OH	6-CH_3	H	H	H	HCl (1:3); H_2O(1:1)
28	B24	CH	4-CH_2OH	3-OH	5-CH_2OH	H	H	HCl (1:1)
192	B27	CH	6-CH_3	H	H	CH_3	H	
299	B16	CH	3-CN	H	H	H	H	mp. 142°C
300	B20	CH	4-OCH_3	3-OCH_3	H	H	$CH(CH_3)_2$	HCl (1:4); H_2O(1:2); mp. 210°C
301	B16	CH	3-NH-SO_2-pheny	6-Cl	H	H	H	mp. 161°C
307	B20	CH	5-OCH_3	6-OCH_3	H	H	$CH(CH_3)_2$	$C_2H_2O_4$ (2:7); mp. 90°C

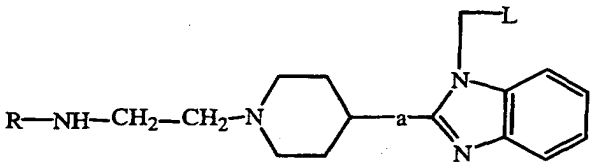
Table 7



Co. No.	Ex. No.	n	*	a	R^a	R^b	R^c	R^d	Physical data
193	B16	2	2	CH_2	H	H	H	H	ethanedioate (1:3); H_2O (1:2); mp. 125°C
194	B22b	1	2	NH	Cl	H	6-CH_3	$CH(CH_3)_2$	
195	B22b	1	2	NH	H	7-CH_3	6-CH_3	$CH(CH_3)_2$	
196	B16	2	2	NH	H	H	H	H	ethanedioate (2:7); H_2O (1:2); mp. 170°C
197	B16	1	2	N(CH_3)	H	H	H	H	
198	B16	1	2	N(CH_2-phenyl)	H	H	H	H	HCl (1:3); H_2O (1:1)
199	B27	0	2	NH	H	H	H	H	HCl (1:4); H_2O (1:2)
200	B1a	1	2	CH_2	OCH_3	6-OCH_3	H	H	HCl (1:4); H_2O (1:1); 2-propanolate (1:1)
201	B1a	1	3	NH	H	H	6-Br	H	HBr (1:4); H_2O (1:4)
202	B16	1	4	NH	H	H	H	H	HCl (1:4); H_2O (1:3)
296	B22b	1	2	NH	CH_3	H	6-CH_3	$CH(CH_3)_2$	-

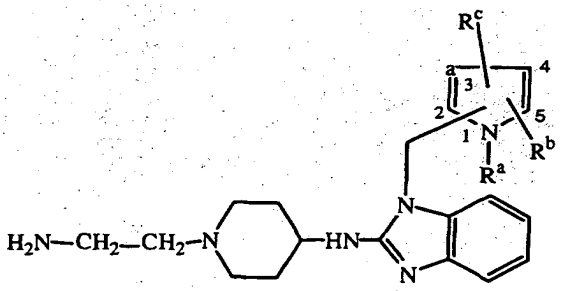
* = position pyridyl

Table 8



Co. No.	Ex. No.	L	a	R	Physical data
203	B16	4-pyrimidinyl	NH	H	HCl (1:4); H_2O (1:2)
204	B16	2-pyrimidinyl	NH	H	HCl (1:3); H_2O (1:1)
205	B16	2-pyrimidinyl	NH	H	
206	B16	3-pyridazinyl	NH	H	HCl (1:3); H_2O (1:1)
207	B16	4,6-dimethoxy-2-pyrimidinyl	NH	H	HCl (1:4); H_2O (1:3)
208	B16	2-pyrimidinyl	NH	H	HCl (1:4); H_2O (1:1)
209	B16	6-methyl-2-pyridyl	$CH[N(CH_3)_2]$	H	HCl (1:4); H_2O (1:2); 2-propanolate (1:1)
210	B7	6-methyl-2-pyridyl	$CH[N(CH_3)_2]$	$-COOC(CH_3)_3$	
211	B25	2-pyridiyl	NH	CH_3	HCl (1:4); H_2O (1:2); mp. 224°C
212	B27	2-[$C(CH_3)_3$]-6-OH-4-pyrimidinyl	NH	H	

Table 9

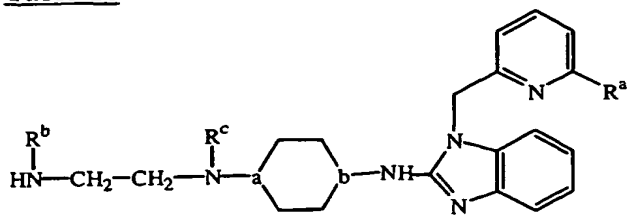


Co. No.	Ex. No.	*	a	R^a	R^b	R^c	Physical data
213	B16	2	N	$CH_2C_6H_5$	H	H	HCl (1:4)
214	B16	5	N	H	4-CH_3	H	HCl (1:4); H_2O (1:3)
215	B16	5	N	CH_3	4-CH_3	H	HCl (1:4); H_2O (1:2)
216	B16	2	N	CH_3	5-$COOC_2H_5$	4-CH_3	HCl (1:4)
217	B16	2	N	CH_3	5-Cl	H	HCl (1:4); H_2O (1:2)
218	B16	5	N	2-propyl	2-SCH_3	H	HCl (1:4); H_2O (1:1)
219	B16	5	N	C_2H_5	2-CH_3	4-CH_3	HCl (1:4); H_2O (1:2); 2-propanolate (1:1)

Co. No.	Ex. No.	*	a	R^a	R^b	R^c	Physical data
220	B16	5	N	CH_3	2-CH_3	4-CH_3	HCl (1:4); H_2O (1:2)
21	B17	2	CH	CH_3	5-CH_3	H	H_2O (1:1)
221	B27	2	CH	CH_3	5-$COOC_2H_5$	H	
222	B27	2	CH	CH_3	5-$COOC_2H_5$	4-Br	

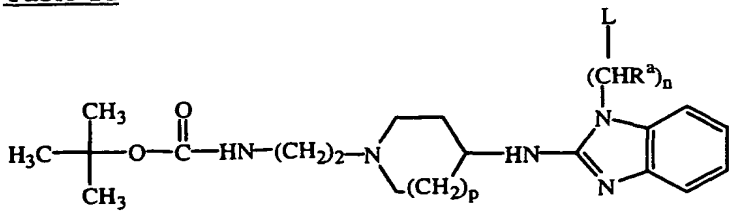
* position monocyclic heterocycle

Table 10



Co. No.	Ex. No.	a	b	R^a	R^b	R^c	Physical data
14	B11	CH	CH	H	$COCH_3$	H	(cis); mp. 126
15	B11	CH	CH	H	$COCH_3$	H	(trans); mp. 200
223	B16	CH	CH	H	H	H	(trans); HCl (1:4); H_2O (1:1); mp. 210
29	B25	CH	N	CH_3	H	H	
224	B25	CH	N	CH_3	H	CH_3	HCl (1:5); H_2O (1:3)

Table 11

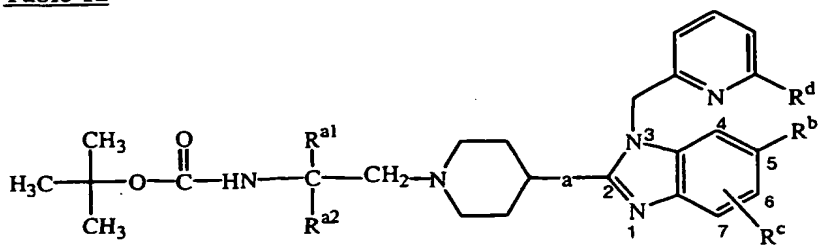


Co. No.	Ex. No.	n	p	R^a	L	Physical data
225	B7	1	1	H	6-chloro-2-pyridyl	
8	B7	1	1	H	6-methyl-2-pyrazinyl	
226	B7	1	2	H	2-pyridyl	
227	B7	1	1	H	5-methyl-2-pyrazinyl	
228	B7	1	1	CH_3	2-pyridyl	
229	B7	1	2	H	2-pyridyl	
230	B7	1	1	H	4-methyl-1*H*-imidazol-5-yl	

Co. No.	Ex. No.	n	p	R[a]	L	Physical data
231	B7	1	1	H	3-methyl-2-pyrazinyl	
232	B7	2	1	H	2-pyridyl	
233	B7	1	1	H	1,4-dimethyl-1*H*-imidazol-5-yl	
234	B7	1	1	H	4-pyrimidinyl	
235	B7	0	1	-	2-pyrimidinyl	
236	B7	1	1	H	6-(hydroxymethyl)-2-pyridyl	
237	B7	1	1	H	1,4-dimethyl-5-(-$COOC_2H_5$)-1*H*-imidazol-2-yl	
238	B7	1	1	CH_3	2-pyrazinyl	
239	B7	1	1	H	3,5,6-trimethyl-2-pyrazinyl	
240	B7	1	1	Ethyl	2-pyrazinyl	
241	B7	1	1	CH_3	6-methyl-2-pyrazinyl	
242	B7	1	1	H	5-chloro-1-methyl-1*H*-imidazol-2-yl	
243	B7	1	1	H	4,6-dimethyl-2-pyridyl	
244	B7	1	1	H	6-bromo-2-pyridyl	
245	B7	1	1	H	6-(-$COOC_2H_5$)-2-pyridyl	
246	B7	1	1	H	1,5-dimethyl-2-pyrrolyl	
247	B7	1	1	H	6-methoxy-2-pyridyl	
248	B7	1	1	H	4-chloro-2-pyridyl	
249	B7	1	1	H	4-methoxy-2-pyridyl	
250	B7	1	1	H	2-pyrimidinyl	
251	B7	1	1	H	3-methoxy-6-methyl-2-pyridyl	
252	B7	1	1	H	6-methyl-3-(-O-C_2H_4-O-C_2H_5)-2-pyridyl	
253	B7	1	1	CH_3	6-hydroxymethyl-2-pyridyl	
254	B7	1	1	H	6-bromo-3-pyridyl	
9	B8	1	1	H	2-(1,1-dimethylethyl)-6-hydroxy-4-pyrimidinyl	
255	B8	1	1	H	1-(phenylmethyl)-1*H*-imidazol-2-yl	
256	B8	1	1	H	1-(2-propyl)-2-(-S-CH_3)-1*H*-imidazol-5-yl	
257	B8	1	1	CH_3	6-chloro-2-pyridyl	
258	B8	1	1	H	1-ethyl-2,4-dimethyl-1*H*-imidazol-5-yl	H_2O (1:1)
259	B8	1	1	H	3-hydroxy-6-methyl-2-pyridyl	
260	B8	1	1	H	4,6-dimethoxy-2-pyrimidinyl	
261	B8	1	1	H	5-(-$COOC_2H_5$)-2-pyrazinyl	
262	B8	1	1	H	1,2,4-trimethyl-1*H*-imidazol-5-yl	
10	B9a	1	1	H	3-(-O-C_2H_4Cl)-6-methyl-2-pyridyl	

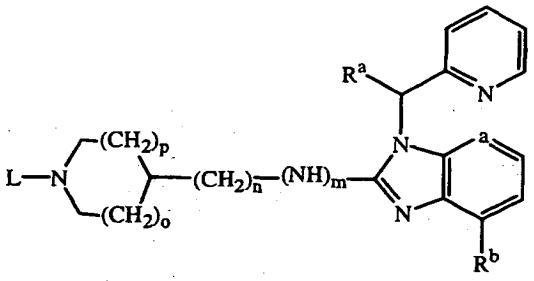
Co. No.	Ex. No.	n	p	R^a	L	Physical data
263	B9a	1	1	H	6-(-CH_2-O-CH_3)-2-pyridyl	
11	B9b	1	1	H	3-[-O-C_2H_4-N(CH_3)$_2$]-6-methyl-2-pyridyl	
12	B10a	1	1	H	6-chloro-3-pyridazinyl	
13	B10b	1	1	H	3-pyridazinyl	

Table 12



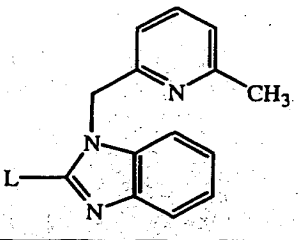
Co. No.	Ex. No.	R^{a1}, R^{a2}	R^b	R^c	a	R^d	Physical data
264	B7	H, H	OCH_3	6-OCH_3	CH_2	H	
265	B7	H, H	H	H	N(CH_3)	H	
266	B7	H, H	H	H	N(CH_2-C_6H_5)	H	
267	B7	H, H	Cl	6-Cl	NH	CH_3	
268	B7	H, H	CH_3	6-CH_3	NH	CH_3	
269	B7	H, H	H	4-Cl	NH	CH_3	
270	B7	H, H	H	7-Cl	NH	CH_3	
271	B7	H, H	H	6-NO_2	NH	CH_3	
272	B7	H, H	NO_2	H	NH	CH_3	
273	B7	H, H	H	7-CH_3	NH	CH_3	
274	B7	H, H	H	4-CH_3	NH	CH_3	H_2O (1:1)
275	B7	H, H	H	6-ethoxy-carbonyl	NH	CH_3	
276	B7	H, H	H	6-hydroxy-methyl	NH	CH_3	
277	B7	H, H	CF_3	H	NH	CH_3	
278	B7	H, H	H	6-CF_3	NH	CH_3	
279	B7	H, H	H	H	NH	-CO-N(CH_3)$_2$	
280	B7	H, H	Cl	H	NH	CH_3	
16	B12	CH_3, CH_3	H	H	NH	H	
17	B13	H, H	-NH_2	H	NH	CH_3	
281	B13	H, H	H	6-NH_2	NH	CH_3	
19	B15	-CH_2OH, H	H	H	NH	H	

Table 13



Co. No.	Ex. No.	n	m	o	p	a	R^a	R^b	L	Physical data
6	B5	1	0	2	1	CH	H	H	H	
283	B27	1	0	1	1	N	H	H	$-(CH_2)_2-NH_2$	HCl (1:4), H_2O (1:1); 2-propanolate (1:1)
284	B27	1	1	1	1	N	H	H	$-(CH_2)_2-NH_2$	HCl (1:1)
285	B27	1	1	0	2	CH	H	H	$-(CH_2)_2-NH_2$	HCl (1:4), H_2O (1:1); mp. 205°C
286	B4	1	1	0	2	CH	H	H	H	
30	B26	0	1	1	1	CH	CH_3	H	$-CH(CH_3)-CH_2-NH_2$	mp. 85°C

Table 14



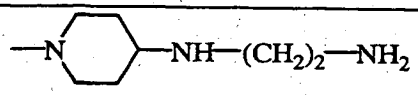
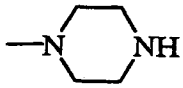
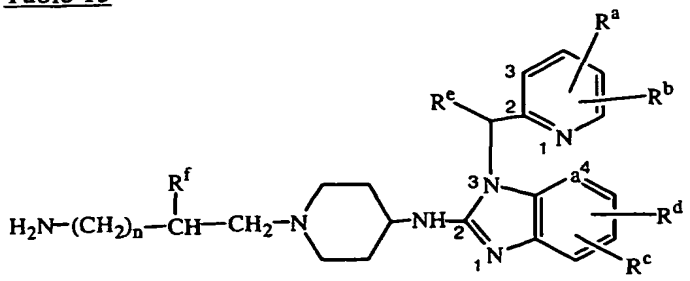
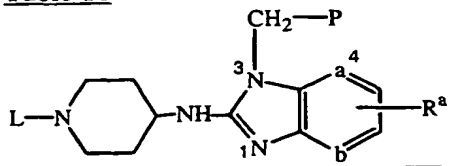
Co. No.	Ex. No.	L	Physical data
288	B25		
289	B4		
309	B19	$-NH-(CH_2)_3-NH_2$	HCl (1:3); H_2O (1:2)

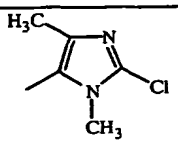
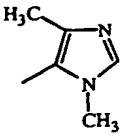
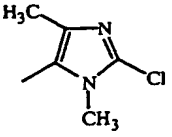
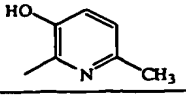
Table 15

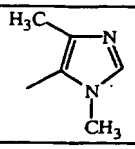


Co. No.	Ex. No.	a	n	R^a	R^b	R^c	R^d	R^e	R^f	Physical data
290	B16	CH	0	3-OH	6-CH_3	7-CH_3	H	H	H	HCl (1:4); H_2O (1:4)
291	B22b	N	0	3-OH	6-CH_3	7-CH_3	H	H	CH-$(CH_3)_2$	-
292	B22b	CH	0	3-OH	6-CH_3	7-CH_3	H	H	CH_3	HCl (1:4); H_2O (1:3)
293	B22b	CH	0	3-OH	6-CH_3	7-CH_3	H	H	CH-$(CH_3)_2$	-
294	B22b	CH	0	6-CH_3	H	7-CH_3	H	H	CH-$(CH_3)_2$	-
303	B28	CH	1	6-CH_3	H	7-CH_3	H	H	OH	H_2O (1:1)
304	B22b	CH	0	6-CH_3	H	6-CH_3	H	H	CH-$(CH_3)_2$	-

Table 16



Co. No.	Ex. No.	a	b	R^a	L	P	Physical data
295	B22b	CH	CH	5-Cl	-CH_2-CH(NH_2)-CH$(CH_3)_2$		
297	B22b	CH	CH	5-Cl	-CH_2-CH(NH_2)-CH$(CH_3)_2$		H_2O (1:1)
298	B22b	CH	CH	H	-CH_2-CH(NH_2)-CH$(CH_3)_2$		
310	B1b	CH	N	H	H		HBr (1:3).H_2O (1:1).C_2H_6O (1:1)

Co. No.	Ex. No.	a	b	R^a	L	P	Physical data
302	B1a	CH	CH	5-Cl	H		

C. Pharmacological example

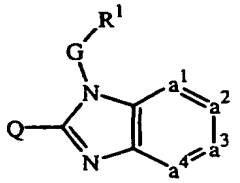
Example C1 : In vitro screening for activity against Respiratory Syncytial Virus.

The percent protection against cytopathology caused by viruses (antiviral activity or IC_{50}) achieved by tested compounds and their cytotoxicity (CC_{50}) were both calculated from dose-response curves. The selectivity of the antiviral effect is represented by the selectivity index (SI), calculated by dividing the CC_{50} (cytotoxic dose for 50% of the cells) by the IC_{50} (antiviral activity for 50 % of the cells).

Automated tetrazolium-based colorimetric assays were used for determination of IC_{50}s and CC_{50}s of test compounds. Flat-bottom, 96-well plastic microtiter trays were filled with 180 µl of Eagle's Basal Medium, supplemented with 5 % FCS (0% for FLU) and 20 mM Hepes buffer. Subsequently, stock solutions (7.8 x final test concentration) of compounds were added in 45 µl volumes to a series of triplicate wells so as to allow simultaneous evaluation of their effects on virus- and mock-infected cells. Five five-fold dilutions were made directly in the microtiter trays using a robot system. Untreated virus controls, and HeLa cell controls were included in each test. Approximately 100 $TCID_{50}$ of Respiratory Syncytial Virus was added to two of the three rows in a volume of 50 µl. The same volume of medium was added to the third row. In this third row, the cytotoxicity of the compounds at the same concentrations as those used to measure the antiviral activity. After two hours of incubation, a suspension (4×10^5 cells/ml) of HeLa cells was added to all wells in a volume of 50µl. The cultures were incubated at 37°C in a 5% CO_2 atmosphere. Seven days after infection the cytotoxicity and the antiviral activity was examined spectrophotometrically. To each well of the microtiter tray, 25 µl of a solution of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) was added . The trays were further incubated at 37°C for 2 hours, after which the medium was removed from each cup. Solubilization of the formazan crystals was achieved by adding 100 µl 2-propanol. Complete dissolution of the formazan crystals were obtained after the trays have been placed on a plate shaker for 10 min. Finally, the absorbances were read in an eight-channel computer-controlled photometer (Multiskan MCC, Flow Laboratories) at two wavelengths (540 and 690 nm). The absorbance measured at 690 nm was automatically subtracted from the absorbance at 540 nm, so as to eliminate the effects of non-specific absorption.

Claims

1. Use of a compound for the manufacture of a medicament for the treatment of viral infections, wherein the compound is a compound of formula



(I)

a prodrug, *N*-oxide, addition salt, quaternary amine, metal complex or stereochemically isomeric form thereof, wherein

$-a^1=a^2-a^3=a^4-$ represents a bivalent radical of formula

-CH=CH-CH=CH- (a-1);

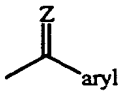
-N=CH-CH=CH- (a-2);

-CH=N-CH=CH- (a-3);

-CH=CH-N=CH- (a-4); or

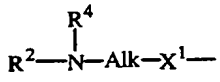
-CH=CH-CH=N- (a-5);

wherein each hydrogen atom in the radicals (a-1), (a-2), (a-3), (a-4) and (a-5) may optionally be replaced by halo, C_{1-6}alkyl, nitro, amino, hydroxy, C_{1-6}alkyloxy, polyhaloC_{1-6}alkyl, carboxyl, aminoC_{1-6}alkyl, mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, hydroxyC_{1-6}alkyl, or a radical of formula

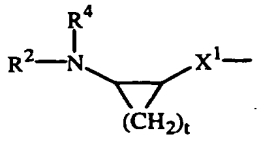


wherein =Z is =O, =CH-C(=O)-$NR^{5a}R^{5b}$, $=CH_2$, =CH-C_{1-6}alkyl, =N-OH or =N-O-C_{1-6}alkyl;

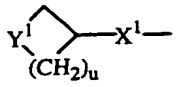
Q is a radical of formula



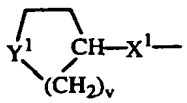
(b-1)



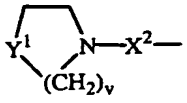
(b-2)



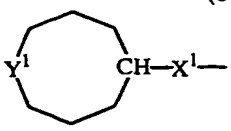
(b-3)



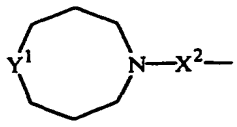
(b-4)



(b-5)



(b-6)



(b-7)

wherein Alk is C_{1-6}alkanediyl;

Y^1 is a bivalent radical of formula $-NR^2-$ or $-CH(NR^2R^4)-$;

X^1 is NR^4, S, S(=O), $S(=O)_2$, O, CH_2, C(=O), $C(=CH_2)$, CH(OH), $CH(CH_3)$, $CH(OCH_3)$, $CH(SCH_3)$, $CH(NR^{5a}R^{5b})$, CH_2-NR^4 or NR^4-CH_2;
X^2 is a direct bond, CH_2 or C(=O);
t is 2, 3, 4 or 5;
u is 1, 2, 3, 4 or 5;
v is 2 or 3; and

whereby each hydrogen atom in Alk and the carbocycles and the heterocycles defined in radicals (b-2), (b-3), (b-4) and (b-5), may optionally be replaced by R^3; with the proviso that when R^3 is hydroxy or C_{1-6}alkyloxy, then R^3 can not replace a hydrogen atom in the α position relative to a nitrogen atom;

G is a direct bond or C_{1-10}alkanediyl;

R^1 is a monocyclic heterocycle selected from pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyrrolyl, imidazolyl and pyrazolyl; and each heterocycle may optionally be substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5a}-, aryl-SO_2-NR^{5a}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5a}R^{5b}$, $HO(-CH_2-CH_2-O)_n$-, halo$(-CH_2-CH_2-O)_n$-, C_{1-6}alkyloxy$(-CH_2-CH_2-O)_n$-, arylC_{1-6}alkyloxy$(-CH_2-CH_2-O)_n$- and mono-or di(C_{1-6}alkyl)amino$(-CH_2-CH_2-O)_n$-;
each n independently is 1, 2, 3 or 4;

R^2 is hydrogen, pyrrolidinyl, piperidinyl, homopiperidinyl, C_{3-7}cycloalkyl substituted with NHR^6, or C_{1-10}alkyl substituted with NHR^6 and optionally with a second, third or fourth substituent selected from amino, hydroxy, C_{3-7}cycloalkyl, C_{2-5}alkanediyl, piperidinyl, mono-or di(C_{1-6}alkyl)amino, C_{1-6}alkyloxycarbonylamino, aryl and aryloxy;

R^3 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy or arylC_{1-6}alkyl;

R^4 is hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl;

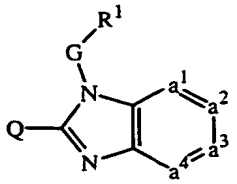
R^{5a} and R^{5b} each independently are hydrogen or C_{1-6}alkyl; or

R^{5a} and R^{5b} taken together from a bivalent radical of formula $-(CH_2)_s-$ wherein s is 4 or 5;

R^6 is hydrogen, C_{1-4}alkyl, formyl, C_{1-6}alkylcarbonyl or C_{1-6}alkyloxycarbonyl;

aryl is phenyl or phenyl substituted with 1 or more, such as 2, 3 or 4, substituents selected from halo, hydroxy, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, polyhaloC_{1-6}alkyl, and C_{1-6}alkyloxy.

2. A compound of formula (I)



(I)

a prodrug, *N*-oxide, addition salt, quaternary amine, metal complex or stereochemically isomeric form thereof, wherein

$-a^1=a^2-a^3=a^4-$ represents a radical of formula

-CH=CH-CH=CH- (a-1);

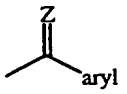
-N=CH-CH=CH- (a-2);

-CH=N-CH=CH- (a-3);

-CH=CH-N=CH- (a-4); or

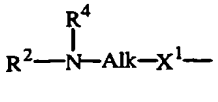
-CH=CH-CH=N- (a-5);

wherein each hydrogen atom in the radicals (a-1), (a-2), (a-3), (a-4) and (a-5) may optionally be replaced by halo, C_{1-6}alkyl, nitro, amino, hydroxy, C_{1-6}alkyloxy, polyhaloC_{1-6}alkyl, carboxyl, aminoC_{1-6}alkyl, mono- or di(C_{1-4}alkyl)amino$_1$alkyl, C_{1-6}alkyloxycarbonyl, hydroxyC_{1-6}alkyl, or a radical of formula

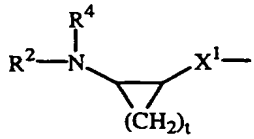


wherein =Z is =O, =CH-C(=O)-$NR^{5a}R^{5b}$, $=CH_2$, =CH-C_{1-6}alkyl, =N-OH or =N-O-C_{1-6}alkyl;

Q is a radical of formula



(b-1)



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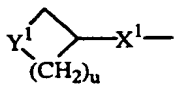

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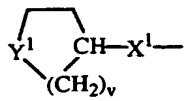
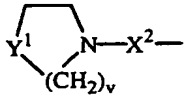
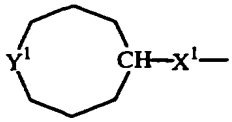


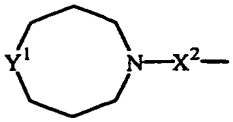
(b-4)



(b-5)



(b-6)



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Y^1 is a bivalent radical of formula $-NR^2-$ or $-CH(NR^2R^4)-$;

X^1 is NR^4, S, S(=O), $S(=O)_2$, O, CH_2, C(=O), $C(=CH_2)$, CH(OH), $CH(CH_3)$, $CH(OCH_3)$, $CH(SCH_3)$, $CH(NR^{5a}R^{5b})$, CH_2-NR^4 or NR^4-CH_2;

X^2 is a direct bond, CH_2 or C(=O);

t is 2, 3, 4 or 5;

u is 1, 2, 3, 4 or 5;

v is 2 or 3; and

whereby each hydrogen atom in Alk and the carbocycles and the heterocycles defined in radicals (b-2), (b-3), (b-4), (b-5), (b-6) and (b-7) may optionally be replaced by R^3; with the proviso that when R^3 is hydroxy or C_{1-6}alkyloxy, then R^3 can not replace a hydrogen atom in the α position relative to a nitrogen atom;

G is a direct bond or C_{1-10}alkanediyl;

R^1 is a monocyclic heterocycle selected from pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyrrolyl, imidazolyl and pyrazolyl; and each heterocycle may optionally be substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di-(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5a}-, aryl-SO_2-NR^{5a}-, C_{1-6}alkyloxyarbonyl, -C(=O)-$NR^{5a}R^{5b}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy-(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino-(-CH_2-CH_2-O)$_n$-;

each n independently is 1, 2, 3 or 4;

R^2 is hydrogen, pyrrolidinyl, piperidinyl, homopiperidinyl, C_{3-7}cycloalkyl substituted with NHR^6, or C_{1-10}alkyl substituted with NHR^6 and optionally with a second, third or fourth substituent selected from amino, hydroxy, C_{3-7}cycloalkyl, C_{2-5}alkanediyl, piperidinyl, mono-or di(C_{1-6}alkyl)amino, C_{1-6}alkyloxycarbonylamino, aryl and aryloxy;

R^3 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy or arylC_{1-6}alkyl;

R^4 is hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl;

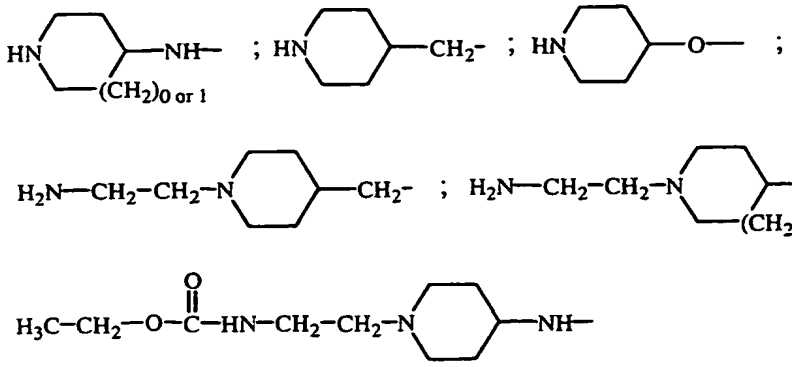
R^{5a} and R^{5b} each independently are hydrogen or C_{1-6}alkyl; or

R^{5a} and R^{5b} taken together from a bivalent radical of formula -$(CH_2)_s$- wherein s is 4 or 5;

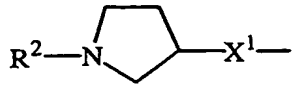
R^6 is hydrogen, C_{1-4}alkyl, formyl, C_{1-6}alkylcarbonyl or C_{1-6}alkyloxycarbonyl;

aryl is phenyl or phenyl substituted with 1 or more, such as 2, 3 or 4, substituents selected from halo, hydroxy, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, polyhaloC_{1-6}alkyl, and C_{1-6}alkyloxy;

provided that when G is methylene, and R^1 is 2-pyridyl, 3-pyridyl, 6-methyl-2-pyridyl, 2-pyrazinyl or 5-methyl-imidazol-4-yl, and =a^1-a^2=a^3-a^4= is =CH-CH=CH-CH= or =N-CH=CH-CH=, then Q is other than

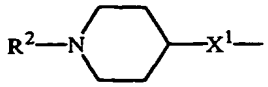


3. A compound as claimed in claim 2 wherein the following restrictions apply :

when Q is 

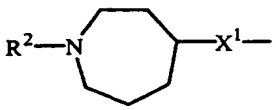
wherein X^1 is NR^4, O, S, S(=O), $S(=O)_2$, CH_2, C(=O), $C(=CH_2)$ or $CH(CH_3)$, then R^1 is other than pyridyl, pyridyl substituted with C_{1-6}alkyl, pyrimidinyl, pyrazinyl, imidazolyl and imidazolyl substituted with C_{1-6}alkyl.

4. A compound as claimed in claim 2 wherein the following restrictions apply :

when Q is 

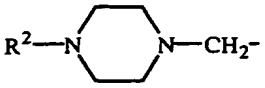
wherein X^1 is NR^4, O, S, S(=O), $S(=O)_2$, CH_2, C(=O), $C(=CH_2)$ or $CH(CH_3)$, then R^1 is other than pyridyl, pyridyl substituted with C_{1-6}alkyl, pyridyl substituted with 1 or 2 C_{1-6}alkyloxy, pyrazinyl, pyrrolyl, pyrrolyl substituted with C_{1-6}alkyl, imidazolyl and imidazolyl substituted with C_{1-6}alkyl.

5. A compound as claimed in claim 2 wherein the following restrictions apply :

when Q is 

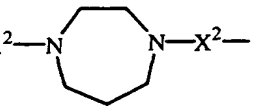
wherein X^1 is NR^4, O, S, S(=O), $S(=O)_2$, CH_2, C(=O), $C(=CH_2)$ or $CH(CH_3)$, then R^1 is other than pyridyl, pyridyl substituted with C_{1-6}alkyl, pyrimidinyl, pyrazinyl, imidazolyl and imidazolyl substituted with C_{1-6}alkyl.

6. A compound as claimed in claim 2 wherein the following restrictions apply :

when Q is 

then R^1 is other than pyridyl, pyrimidinyl, pyrazinyl, imidazolyl and imidazolyl substituted with C_{1-6}alkyl.

7. A compound as claimed in claim 2 wherein the following restrictions apply :

when Q is 

wherein X^2 is CH_2 or a direct bond, then R^1 is other than pyridyl, pyridyl substituted with C_{1-6}alkyl, pyrimidinyl, pyrazinyl, imidazolyl and imidazolyl substituted with C_{1-6}alkyl.

8. A compound as claimed in anyone of claims 2 to 7 for use as a medicine.

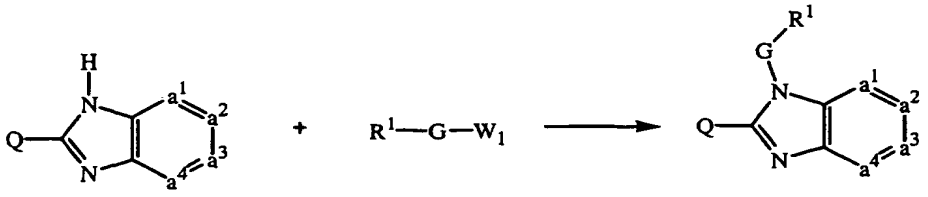
9. Use of a compound as claimed in claim 1 wherein said viral infection is a respiratory syncytial virus infection.

10. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredient a therapeutically effective amount of a compound as claimed in claim 2.

11. A process of preparing a composition as claimed in claim 10 characterized in that a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound as claimed in claim 2.

12. A process of preparing a compound as claimed in claim 2, characterized by

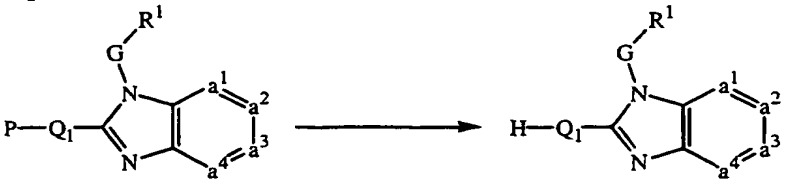
a) reacting an intermediate of formula (II-a) with an intermediate of formula (III)



(II-a) (III) (I)

with R^1, G, Q and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and W_1 being a suitable leaving group, in the presence of a suitable base and in a suitable reaction-inert solvent;

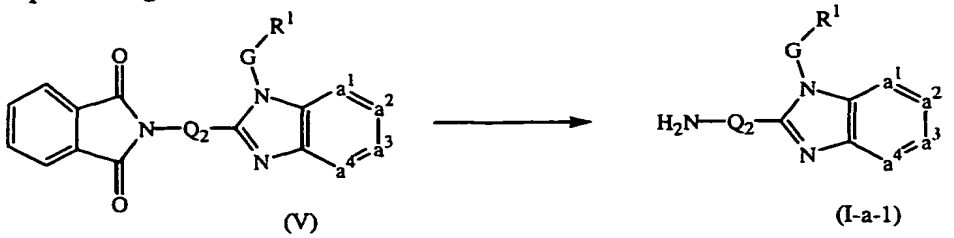
b) deprotecting an intermediate of formula (IV)



(IV) (I-a)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, H-Q_1 being defined as Q according to claim 2 provided that R^2 or R^6 is hydrogen, and P being a protective group;

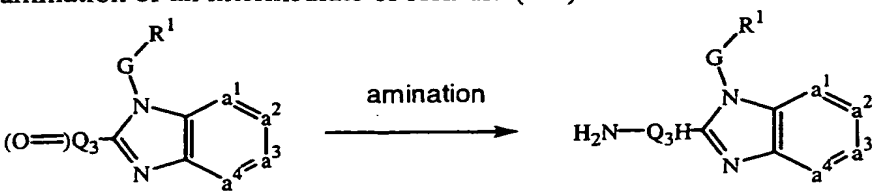
c) deprotecting an intermediate of formula (V)



(V) (I-a-1)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and H_2N-Q_2 being defined as Q according to claim 2 provided that R^6 is hydrogen or R^2 and R^4 are both hydrogen;

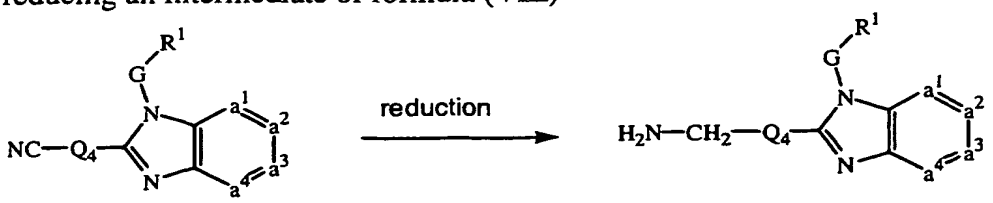
d) amination of an intermediate of formula (VII)



(VII) (I-a-1-1)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and H_2N-Q_3H being defined as Q according to claim 2 provided that R^6 is hydrogen or R^2 and R^4 are both hydrogen, and the carbon adjacent to the nitrogen carrying the R^6, or R^2 and R^4 substituents contains at least one hydrogen, in the presence of a suitable amination reagent;

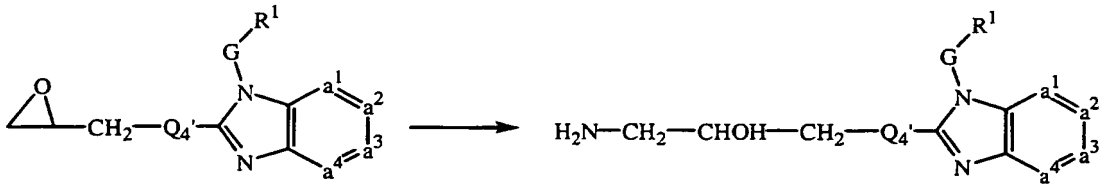
e) reducing an intermediate of formula (VIII)



(VIII) (I-a-1-2)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and $H_2N-CH_2-Q_4$ being defined as Q according to claim 2 provided that Q comprises a $-CH_2-NH_2$ moiety, in the presence of a suitable reducing agent;

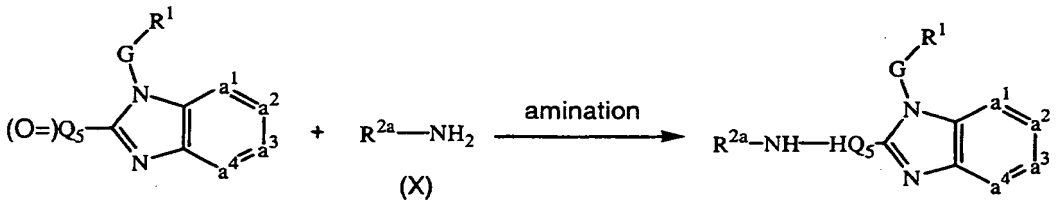
f) amination of an intermediate of formula (LIV)



(LIV) (I-a-1-2-1)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and $H_2N-CH_2-CHOH-CH_2-Q_4$ being defined as Q according to claim 2 provided that Q comprises a $CH_2-CHOH-CH_2-NH_2$ moiety, in the presence of a suitable amination reagent;

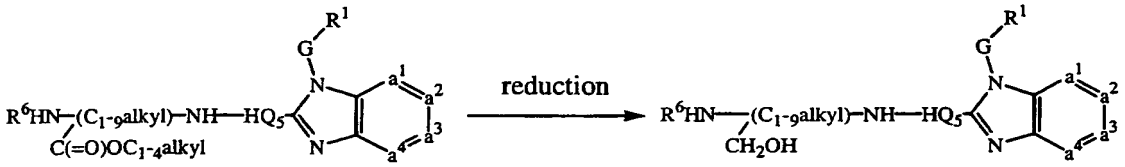
g) amination of an intermediate of formula (IX) by reaction with an intermediate of formula (X)



(IX) (X) (I-b)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and $R^{2a}-NH-HQ_5$ being defined as Q according to claim 2 provided that R^2 is other than hydrogen and is represented by R^{2a}, R^4 is hydrogen, and the carbon atom adjacent to the nitrogen atom carrying the R^2 and R^4 substituents, carries also at least one hydrogen atom, in the presence of a suitable reducing agent;

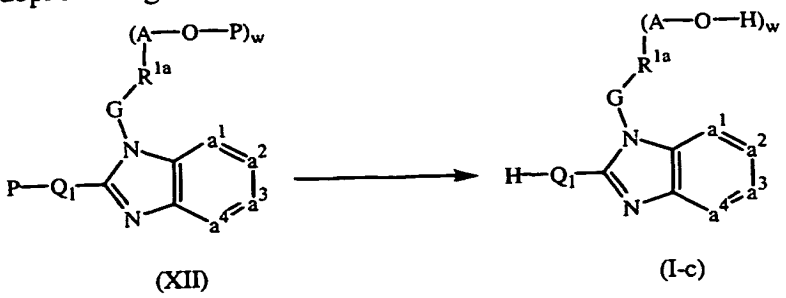
h) reducing an intermediate of formula (XI)



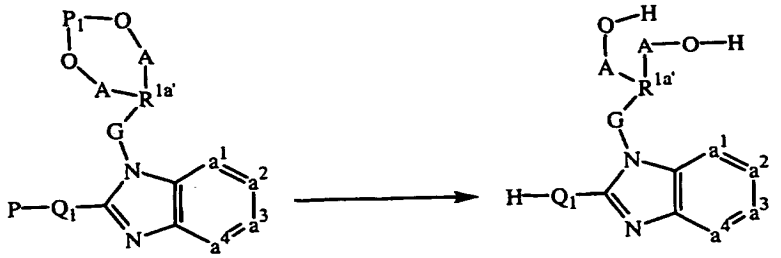
(XI) (I-b-1)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and $R^6HN-[(C_{1-9}alkyl)CH_2OH]-NH-HQ_5$ being defined as Q according to claim 2 provided that R^2 is other than hydrogen and is represented by C_{1-10}alkyl substituted with NHR_6 and with hydroxy, and the carbon atom carrying the hydroxy, carries also two hydrogen atoms, and provided that R^4 is hydrogen, and the carbon atom adjacent to the nitrogen atom carrying the R^2 and R^4 substituents, carries also at least one hydrogen atom, with a suitable reducing agent;

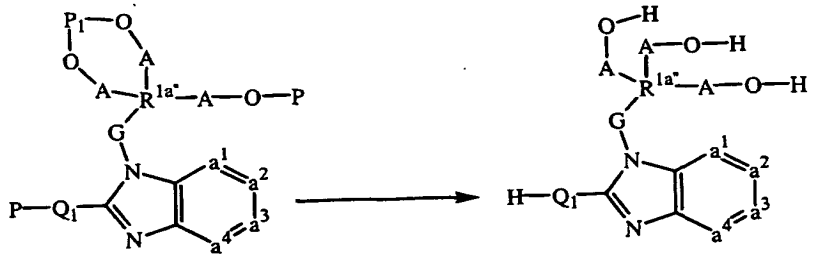
i) deprotecting an intermediate of formula (XII), (XII-a) or (XII-b)



(XII) (I-c)



(XII-a) (I-c-1)



(XII-b) (I-c-2)

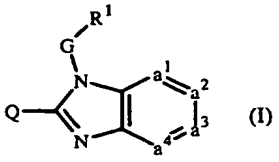
with G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and H-Q_1 being defined as Q according to claim 2 provided that R^2 or R^6 is hydrogen, and R^{1a}-(A-O-H)$_w$, $R^{1a'}$-(A-O-H)$_2$ and $R^{1a''}$-(A-O-H)$_3$ being defined as R^1 according to claim 2 provided that R^1 is substituted with hydroxy, hydroxyC_{1-6}alkyl, or HO(-CH_2-CH_2-O)$_n$-, with w being an integer from 1 to 4 and P or P_1 being a suitable protecting group, with a suitable acid.

and, if desired, converting compounds of formula (I) into each other following art-known transformations, and further, if desired, converting the compounds of formula (I), into a therapeutically active non-toxic acid addition salt by treatment with an acid, or into a therapeutically active non-toxic base addition salt by treatment with a base, or conversely, converting the acid addition salt form into the free base by treatment with alkali, or converting the base addition salt into the free acid by treatment with acid; and, if desired, preparing stereochemically isomeric forms or *N*-oxide forms thereof.

ABSTRACT

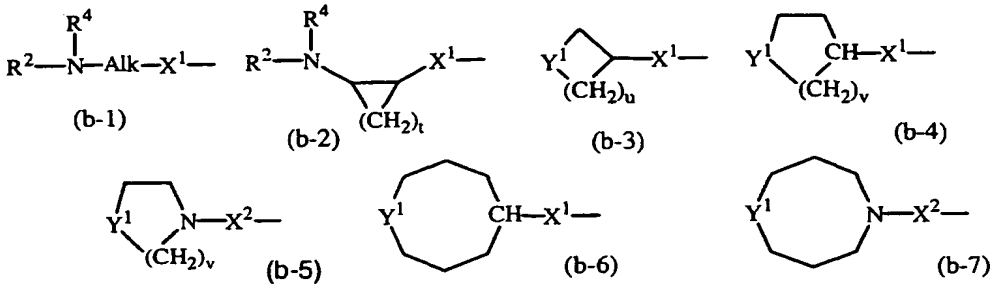
RESPIRATORY SYNCYTIAL VIRUS REPLICATION INHIBITORS

This invention concerns the compounds of formula



(I)

prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes or stereochemically isomeric forms thereof wherein $-a^1=a^2-a^3=a^4-$ is a radical of formula -CH=CH-CH=CH-, -N=CH-CH=CH-, -CH=N-CH=CH-, -CH=CH-N=CH-, -CH=CH-CH=N- wherein each hydrogen atom may optionally be substituted; Q is a radical of formula



(b-1) (b-2) (b-3) (b-4) (b-5) (b-6) (b-7)

wherein Alk is C_{1-6}alkanediyl; Y^1 is a bivalent radical of formula $-NR^2-$ or $-CH(NR^2R^4)-$; X^1 is NR^4, S, S(=O), $S(=O)_2$, O, CH_2, C(=O), $CH(=CH_2)$, CH(OH), $CH(CH_3)$, $CH(OCH_3)$, $CH(SCH_3)$, $CH(NR^{5a}R^{5b})$, CH_2-NR^4 or NR^4-CH_2; X^2 is a direct bond, CH_2 or C(=O); t is 2 to 5; u is 1 to 5; v is 2 or 3; and whereby each hydrogen in Alk and in (b-2), (b-3), (b-4) and (b-5), may optionally be replaced by R^3; provided that when R^3 is hydroxy or C_{1-6}alkyloxy, then R^3 can not replace a hydrogen atom in the α position relative to a nitrogen atom; G is a direct bond or C_{1-10}alkanediyl; R^1 is an optionally substituted monocyclic heterocycle; R^2 is hydrogen, pyrrolidinyl, piperidinyl, homoiperidinyl, C_{3-7}cycloalkyl or C_{1-10}alkyl substituted with NHR^6 and optionally with another substituent; R^3 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy or $aryl_1$-alkyl; R^4 is hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl; R^{5a} and R^{5b} each independently are hydrogen or C_{1-6}alkyl; or R^{5a} and R^{5b} taken together from a bivalent radical of formula $-CH_2)_s-$ wherein s is 4 or 5; R^6 is hydrogen, C_{1-4}alkyl, formyl, C_{1-6}alkylcarbonyl or C_1-alkyloxy-arbonyl; aryl is optionally substituted phenyl; provided that when G is methylene, and R^1 is 2-pyridyl, 3-pyridyl, 6-methyl-2-pyridyl, 2-pyrazinyl or 5-methyl-imidazol-4-yl, and $=a^1-a^2=a^3-a^4=$ is =CH-CH=CH-CH= or =N-CH=CH-CH=, then Q is other than some of the selected piperidine derivatives; as respiratory syncytial virus replication inhibitors; their preparation, compositions containing them and their use as a medicine.